EMERGING ROLE OF MONO&COMBINATION THERAPY OF VILDAGLIPTIN IN ASSESSING THE SAFETY &EFFICACY IN TYPE-2 DIABETIC PATIENTS

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PHARMACY PRACTICE

Submitted By

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ABBREVIATIONS

Abbreviation	Full Form
DM	Diabetic mellitus
T_2DM	Type 2 diabetes
AE	Adverse event
SAEs	Serious Adverse event
PI	Proinsulin
IRI	Immunoreactive insulin
IDDM	Insulin dependent diabetes mellitus
NIDDM	Non-insulin dependent diabetes mellitus
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
DPP4	Dipeptidyl peptidase 4
TZDs	Thiazolidinediones
SU	Sulfonylurea
IGT	Impaired glucose tolerance
HbA1c	Glycosylated hemoglobin
FPG	Fasting plasma glucose
RBS	Random blood sugar
MOA	Mechanism of action
CV	Cardio vascular

OHA	Oral hypoglycemic agents
LDL	Low density lipoprotein
VLDL	Very low density lipoprotein
HDL	High density lipoprotein
TC	Total cholesterol
LFT	Liver function test
ALT	Alanine transaminase
AST	Aspartate transaminase
ULN	Upper limit of the normal
GDM	Gestational diabetic melitus
IFG	Impaired fasting glucose
ADA	American diabetic association
ESRD	End stage renal disease
G6PD	Glucose 6-phosphate dehydrogenase
AMP	Adinosine monophosphate
AMPK	Adinosine monophosphate activated protein kinase

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This is to certify that the dissertation work entitled **"EMERGING ROLE OF MONO&COMBINATION THERAPY OF VILDAGLIPTIN IN ASSESSING THE SAFETY & EFFICACY IN TYPE-2 DIABETIC PATIENTS"** is the bonafide work carried out by **Mr. SALAHUDDHEEN.K**, under the Guidance and supervision of **Mr. S.KANNAN, M.Pharm, (PhD)., Professor & Head,** Department of Pharmacy Practice, JKK MUNIRAJAH MEDICAL RESEARCH FOUNDATION, COLLEGE OF PHARMACY, Komarapalayam.

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DECLARATION

The work presented in this dissertation entitled **"EMERGING ROLE OF MONO & COMBINATION THERAPY OF VILDAGLIPTIN IN ASSESSING THE SAFETY & EFFICACY IN TYPE-2 DIABETIC PATIENTS"** was carried out by me, under the guidance of, **Mr. S.KANNAN ,M.Pharm, (PhD)., Professor & Head** ,Department of Pharmacy Practice, J.K.K.Munirajah Medical Research Foundation College of Pharmacy, Komarapalayam.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other university.

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DEDICATED TO MY PARENTS
AND FRIENDZ

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INTRODUCTION

Epidemiology

Diabetes mellitus one of the most common and chronic disorder in world. But no one is not bothered about its severity & co-morbidity disorders. It increase the prevalence of diabetes is rapidly increasing in the world in a distressing rate, diabetes affect both developed and developing countries. Worldwide DM is currently estimated 368 million, 346 million in 2011& to affect 285 million (6.4%) adults aged 20–79 years and this number is projected to increase to 439 million (7.7%) adults by the year 2030 . Diabetes Atlas 2009 published by the International Diabetes Federation estimated diabetic population in India to around 50.8 million, which is expected to rise to 87 million by 2030, as per these calculation India will be a diabetes capital of the world. Type 2 diabetes (T_2DM) accounts for approximately 85–95% of total reported cases of diabetes (Diabetes atlas). T_2DM is a multifaceted disease involving lot of pathophysiological problems, it includes impaired islet function and insulin resistance, which results in impaired glucose tolerance and inappropriately increase fasting hepatic glucose production. Chances of developing T2DM are increased by obesity and physical inactivity and are further augmented with age.

Definition

Diabetes is a complex and a multivarious group of disorders that disturbs the metabolism of carbohydrates, protein and fat (Kahn CR&

Shechter 1991, Bliss M 2000) characterized by increased fasting (>110 mg/dL) and postprandial blood sugar (>140mg/dL) levels.

Classification of diabetes

Diabetes mellitus is classified into two types- type I (insulin dependent diabetes mellitus, IDDM) and type II (non-insulin dependent diabetes mellitus, NIDDM). IDDM or juvenile onset diabetes is due to cell mediated autoimmune destruction of the β-cells of the pancreas (Aikinson MA& McLaren NK 1994, De-Fronzo 2009) However, NIDDM or adult-onset diabetes results from the development of insulin resistance and the affected individuals usually have insulin deficiency (Takeshi K, Shoichi N 2002) Patients suffering from type I are therefore totally dependent on external source of insulin but patients with Type II diabetes can be treated with dietary changes, exercise and medication

Two most important unmet needs for the management of T_2DM are the lack of lasting efficacy in the reduction of increased glucose level and it fail to target primary causes. Poor glycemic control leads to increased morbidity, mortality and economics associated with T_2DM (Turner RC *et al*., Ohkubo Y *et al* 1995., Koro CE *et al*., 2000) Though Lifestyle modification (Exercise, dietary management) provides the basis for metabolic control of patients with T_2DM, but with diet modification is not enough to attain the normal blood sugar, need for introduction of anti-hyperglycemic agents.

Type 1 diabetes

Insulin-dependent diabetes, juvenile diabetes, Type 1 diabetes is characterized by cellular-mediated autoimmune destruction of islet ß-cells.

Markers:

- Islet cell antibodies (ICAs)
- Auto-antibodies to insulin (IAAs)
- Auto-antibodies to Glutamic Acid Decarboxylase (GAD65)
- Auto-Antibodies to Tyrosine phosphatases IA-2 and IA-2ß

Laboratory findings:

- Hyperglycemia
- Ketonuria (presence of ketone bodies in urine)
- Serum insulin & C-peptide levels
- Auto-antibodies

Type 2 diabetes

Type 2 diabetes is due to insulin insensitivity along with a failure of insulin secretion to overcome this by hyper secretion, resulting in relative insulin deficiency. Type 2 diabetes is more common in individuals with family history of the disease, in individuals with hypertension.

The risks of Type 2 diabetes are:

- Family history of diabetes
- Obesity
- Age $\geq$ 45 years

- Previously identified IFG or IGT
- Hypertension
- Reduced physical activity
- History of gestational diabetes mellitus (GDM) or delivery of babies >4, 5 kg

Sign & Symptoms of diabetes mellitus

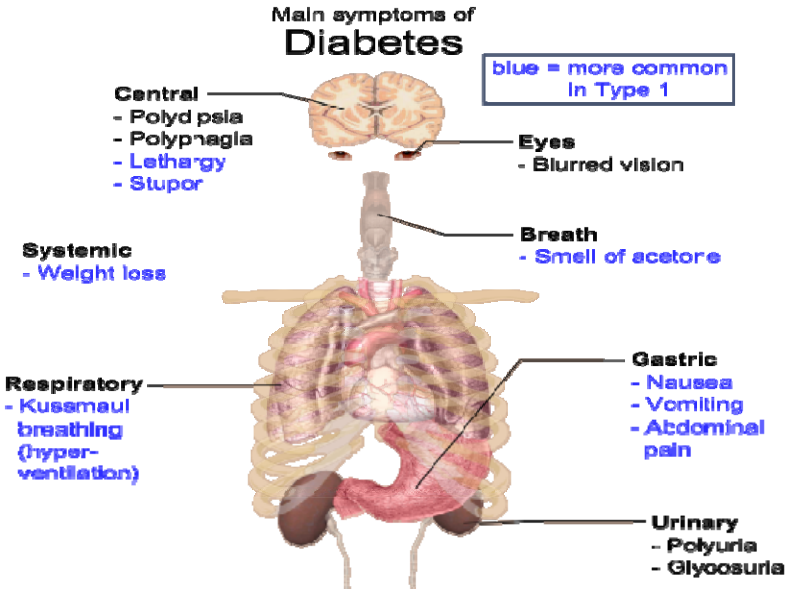
Symptoms may develop quite rapidly (weeks or months) in type 1 diabetes, particularly in children.

- Fatigue
- Increased thirst
- Increased urination
- Nausea
- Vomiting
- Weight loss
- Diabetic ketoacidosis
- Kussmaul breathing
- Abdominal pain

However, in type 2 diabetes symptoms usually develop much more slowly.

- Increased fatigue

- Polydipsia
- Polyuria
- Polyphagia
- Poor wound healing
- Blurry vision
- Irritability
- Infections
- Weight fluctuation



Diagnosis of diabetes

The diagnosis of diabetes mellitus requires the identification of a glycemic cut point, which discriminates normal's from diabetic patients, the present cut points reflect the level of glucose above which microvascular complications have been shown to increase.

Criteria for the Diagnosis of Diabetes Mellitus

Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)

or

2-hour post load glucose ≥200 mg/dL (11.1 mmol/L)

Diagnosis of diabetes is based on:

- Typical symptoms of DM (Polyuria, Polydipsia, and weight loss).
- Fasting plasma glucose > 126 mg/dL (7 mmol/L).
- 2-h post load plasma glucose > 200 mg/dL (11.1 mmol/L)
- Casual (random) plasma glucose > 200 mg/dL (11.1 mmol/L). (ADA 1995)

The pathophysiology of T_2DM

T_2DM as a progressive, complex metabolic disorder characterized by coexisting defects of multiple organ sites it includes insulin resistance in adipose tissue & muscle, is a progressive decline in pancreatic insulin

production, unrestrained hepatic glucose production, and other hormonal deficiencies, other defects include accelerated gastric emptying in patients with T_2DM, especially those who are obese or long duration of diabetic history (Bertin E *et al*., 2001, Weytjens C *et al.,* 1998).

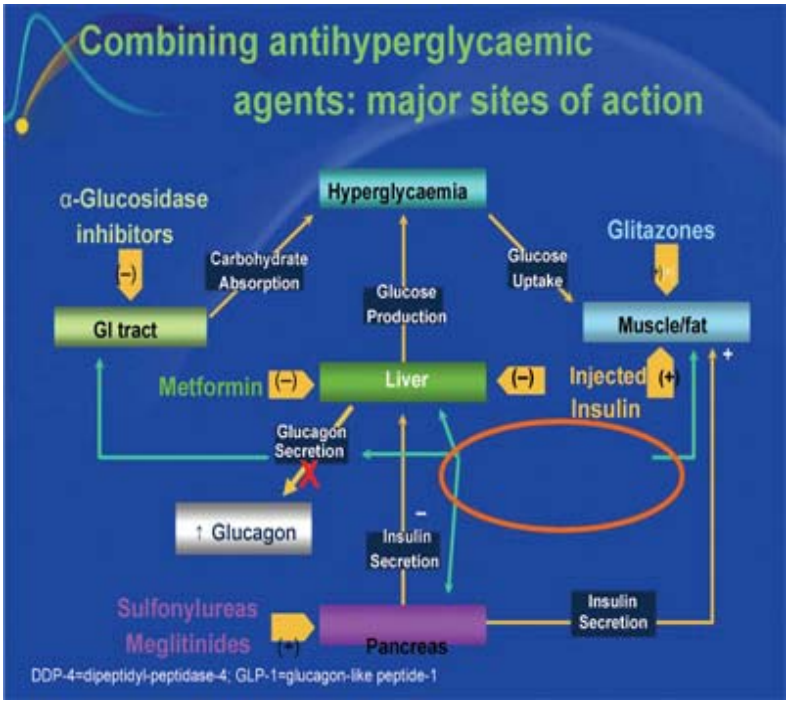
Hormonal deficiencies in T_2DM are due to abnormalities in the production of hormones by beta-cell & its hormone amylin, the alpha-cell hormone glucagon, and the incretin hormones Glucagon-like peptide 1/8 (GLP-1) & glucose-dependent insulinotropic polypeptide (GIP). (Fonseca *et al*., 2007) In addition to the triumvirate of core defects associated with T_2DM (involvement of the pancreatic beta cell, muscle, and liver), other mechanisms of disease onset have been advanced, including accelerated lipolysis, hyperglucagonemia, and incretin deficiency/resistance also, the rate of basal hepatic glucose production is markedly increased in patients with T_2DM, which is closely correlated with elevations in fasting plasma glucagon concentration (DeFronzo *et al*., 1997).

The incretin effect the intestinal augmentation of secretion of insulin attributed to GLP-1 and GIP is reduced in patients with T2DM

The secretion of GIP may be normal or elevated in patients with T2DM while the secretion of GLP-1 is deficient; however, cellular responsiveness to GLP-1 is preserved while responsiveness to GIP is diminished. (Heimesaat MM *et al*., 1994) Both endogenous and exogenous GLP-1 and GIP are degraded in vivo and in vitro by the enzyme DPP-4. The

role of DPP-4 in the immune system stems from its exo-peptidase activity and its interactions with various molecules, including cytokines and chemokines

Different classes of Oral Hypoglycemic Agents (OHA's) are now available that target the different pathophysiologic factors contributing to T_2DM: acarbose containing group delays carbohydrate absorption from intestine, metformin group (biguanides) are mainly target hepatic insulin resistance, pioglitazone group (thiazolidinediones) (TZDs) are targeting adipocyte and muscle insulin resistance and insulin secretagogues or sulfonylureas (SU) are targeted to improved insulin secretion by pancreatic beta cells (Cheng AY *et al.,* 2005) . All the above mentioned classes have nearly equipotent efficacy; however, almost all of them are showing their own kind of adverse events. (Inzucchi SE *et al.,* 2002). The SU therapy shows two major adverse effects like weight gain and hypoglycemia (decreased blood sugar below normal). In the total diabetic patients 80% to 90% of people with diabetes are obese and SUs worsen this condition (increased weight gain), it ranges from 2 to 5 kg and SU cause hypoglycemia affects the elder peoples those with irregular meal schedules (Zimmerman *et al.,* 1997, Schade *et al.,*1998, Kilo *et al.,*1992*)*



Among the new type of oral anti diabetic therapies the DPP-4 inhibitor vildagliptin shows very efficacious drug in reducing blood sugar in a wide range of T_2DM patients, ranging from the impaired glucose tolerance (IGT) population to patients with advanced disease on insulin. Vildagliptin is consider as a second-line treatment option as a part of an oral combination therapy regimen in T_2DM patients those increasing blood sugar is poorly controlled by monotherapy with metformin, a SU or a TZDs. Existing data indicates that HbA1c lowering potential of Vildagliptin also in range of TZDs and acarbose, with sustained reductions to clinically significant levels for up to 2 years. When used as monotherapy or in combination with metformin or insulin, it shows modest reductions in HbA1c values have been showed in patients those using vildagliptin.

T_2DM is a disease due to the progressive decreasing of β-cell function. Unlike many other antihyperglycemic medications, oral inhibitor of DPP-4 vildagliptin improves glycemic control in patients with T_2DM through physiological mechanisms that result in an attenuation of β-cell decline and thus restoration of the incretin effect (Nauck *et al.,* 1986, Drucker *et al.,* 2003, Ahrén B 1994, Ahren B 2006).

Complication

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease. Themain"macrovascular"diseases (relatedto atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease.

Diabetes also causes "microvascular" complications damage to the small blood vessels. Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to visual symptoms, reduced vision, and potentially blindness. Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact

of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.

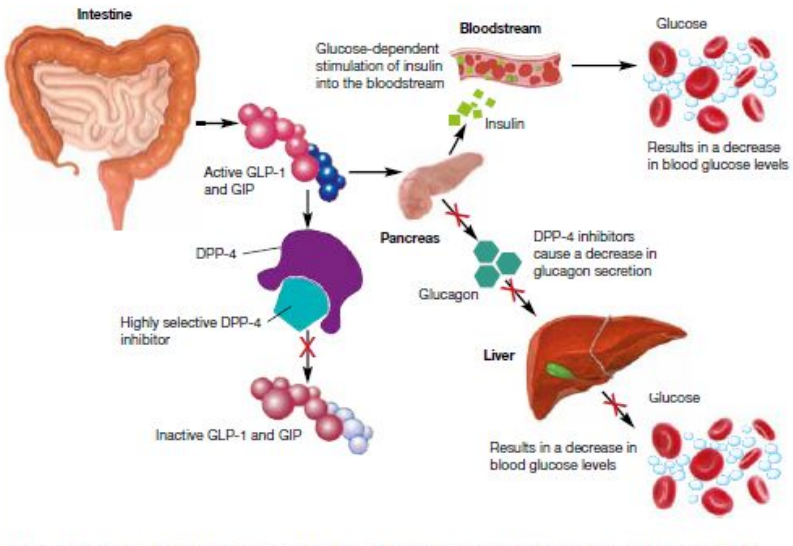
Vildagliptin

The DPP-4 inhibitor vildagliptin is potent, selective and orally active 2nd generation inhibitor of DPP-4, with a reversible and competitive mechanism of action. Vildagliptin binds and forms a complex with DPP-4, causing the inhibition of Dipeptidyl peptidase-4 (Brandt *et al.,* 2005). This cause in improved glycemic control as calculated by Glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels. Vildagliptin presents several advantages over other anti-diabetic medications. Vildagliptin enhances α-cell responsiveness by suppressive action on hyperglycemia & stimulatory action on hypoglycemia.These effects contribute to the efficacy of vildagliptin to improve glycemic control as well as to its low hypoglycemic potential (Schweizer A *et al*., 2009). The effect of improving postprandial blood sugar provides a good alternative treatment option than that of former available drug therapies.

Vildagliptin have generally well acceptance as monotherapy & in combination with other oral hypoglycemic agents. Especially combination of vildagliptin+ metformin shows highly beneficial lowering effects on Glycosylated haemoglobin, fasting blood sugar, random blood sugar. The

major role of an anti diabetic is to reduce the blood sugar only. But in some cases vildagliptin shows some subsidiary effects on lipid profile lowering like low density lipoprotein (LDL), very low density lipoprotein (VLDL), useful high density lipoprotein (HDL) increasing effect, and total cholesterol (TC) lowering, it's side effect reporting also very low to compare with other anti diabetic drugs available in market.

Figure. Concentrations of active GLP-1 and GIP hormones are increased by DPP-4 inhibition, thereby increasing and prolonging the actions of these hormones.



Abbreviations: DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

Vildagliptin have unique mechanism of action allows a lot of combination regimens for effective control of glucose levels. Combining drug with other drugs with complementary mechanism of action makes us to provide a better therapeutic option for T2DM. Vildagliptin is highly beneficial

in combination with metformin or thiazolidinediones, with most important combination of drug being with metformin, because of it's pathogenic point of view combination with metformin principally targeting insulin resistance with vildagliptin primarily targeting the β-cell is a rational approach. In add-on therapy to metformin, vildagliptin shows better blood sugar control than other drugs available in market(Rosenstock *et al.,* 2007)and in an active comparator non inferiority trial, it was shown to be as effective as pioglitazone (Garber AJ *et al.*,2007). Also in other combination trials, vildagliptin as add-on therapy to insulin (Bosi *et al.,* 2007), glimepiride (Fonseca *et al*., 2008) and pioglitazone (Schweizer *et al*., 2007) provided more effective glycemic control.

DPP4 inhibitor (vildagliptin) was commonly well tolerated as monotherapy & combination therapy with other oral hypoglycemic agents. Adverse events shows by vildagliptin are generally of mild or moderate in nature, not that much Sevier and will be vanished in near future. The chance of occurrence of hypoglycemia due to vildagliptin treatment were least and when add on therapy to other oral hypoglycemic agents like metformin, pioglitazone or glibenclamide , the chances for the occurrence of hypoglycemia was not aggravated. And vildagliptin shows a weight-neutral and does not aggravate this problem as many of the antihyperglycemic agents.

The vildagliptin daily dose recommend as 100mg, and it administered as once daily or taken as two divided dose of 50mg in morning and night. When used in dual combination with sulfonylurea, the recommend dose of vildagliptin is 50mg once daily administered in the morning. Drug can be administered with or without meals. The preliminary evidence of beneficial

effects of Vildagliptin, member of the novel class of DPP-4 inhibitors, presents it to be an effective and safe antihyperglycemic agent. It has the potential to significantly change the clinical management of diabetes and can be an effective strategy to prevent or delay progression from the prediabetic state to over T_2DM.

Type-2 diabetic melitus is shows some sort of increased risk of organ complications like cardio vascular disease, hepatitis-C infection and pancreatitis & these complications could be aggravated by drug treatment. Subsequently alongside efficacy, safety profile of any new OHA is very important for the treatment of some chronic and progressive disease like type-2 diabetic melitus. Vildagliptin tolerability profile was reviewed previously. The major reported adverse drug reaction are of mild to moderate severity and transient in nature (Bolli G *et al.,* 2008, Scherbaum *et al.,*2008, Schweizer A *et al.,*2009) with rare treatment related discontinuations.

Side effect- tremor, headache, dizziness, low blood sugar, nausea and weakness. Patients taking vildagliptin may also experience weight gain and swelling the ankles of legs, this is because of increased fluid retention. Fatigue and constipation

Precaution- should care on patients with type 1 diabetes or the patient under treatment for ketoacidosis. Caution in patient under haemodialysis. It is very harmful in patients with liver disorders, those patients with pre-treatment ALT or AST > 3x ULN. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically

thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue it. Following withdrawal of treatment with vildagliptin and LFT normalisation, treatment with vildagliptin should not be reinitiated. Monitoring for skin disorders, such as blistering or ulceration, is recommended while keeping with routine care of the diabetic patient.

Drug interaction- Increased risk of hypoglycemia when used with other anti-diabetic agents thus dose adjustments may be required.

Contraindication- Hypersensitivity, Renal Disease (serum creatinine levels ≥1.5 mg/dL (>135 micromol/L) in males and ≥1.4 mg/dL (>110 micromol/L) in females or abnormal creatinine clearance, which may also result from conditions eg, cardiovascular collapse (shock), acute myocardial infarction and septicemia , Congestive Heart Failure, Diabetic Ketoacidosis

Advantage- DPP-4 inhibitors appear to be extraordinarily well tolerated. Unlike traditional secretagogues (sulphonylureas and glinides), they seem unable to induce hypoglycemia, even at the highest doses.

Disadvantage- Comparing the to other gliptins, vildagliptin has the disadvantage of being a twice daily medicine and being contraindication in hepatic impairment (including patients with pre-treatment Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)> 3x the upper limit of normal) with the small benefit of a combination product**.**

Pioglitazone

Pioglitazone hydrochloride, a thiazolidinediones compound, is a new therapeutic agent for the treatment of type2 diabetes that reduces insulin resistance by enhancing insulin action in skeletal muscle, liver, and adipose tissue. (Whitcomb RW *et al.,* 1971)The mechanism of action of the thiazolidinediones class has yet to be fully elucidated although mechanistic studies indicate that thiazolidinediones influence several process es to increase cell sensitivity to insulin (Saltiel AR *et al.,* 1996, Grossman SL *et al.,*1997), including activation of peroxisome proliferator–activated receptor and alteration Of hepatic glucose metabolism (Ciraldi TP *et al*.,1995, Spiegelman 1998).

Pioglitazone having ability to reduce abnormal blood glucose level, increased insulin, and hypertriglyceridemia & it is characterized by insulin resistance (Sugiyama Y *et al*., 1990, Kemnitz JW *et al*., 1994). Pioglitazone shows metabolic changes by improving insulin response to tissues & it is observed in lot of models insulin resistance. Pioglitazone reduces insulin resistance by enhancing the action of insulin, thereby promoting glucose utilization in peripheral tissues, suppressing gluconeogenesis, and reducing lipolysis (Matthaei S *et al*.,2000, Miyazaki Y *et al*., 2002).

Side effects-feeling short of breath, even with mild exertion, swelling or rapid weight gain, chest pain, general ill feeling nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin)

Precaution- medical history, especially of: heart disease (such as congestive heart failure, chest pain), diabetic ketoacidosis, liver disease, fluid in your lungs, swelling (edema), anemia, a certain eye problem (macular edema). May experience blurred vision, dizziness, or drowsiness due to extremely low or high blood sugar levels. Do not drive, use machinery, or do any activity that requires alertness or clear vision until you are sure you can perform properly.

Drug interaction -two drugs known to have a major interaction with pioglitazone. They are leflunomide, gatifloxacin

Contraindication- Pioglitazone cannot be used in patients with a known hypersensitivity to pioglitazone, other thiazolidinediones or any of components of its pharmaceutical forms. It is ineffective and possibly harmful in diabetes mellitus type 1 and diabetic ketoacidosis acute diseases of the liver are regarded as a contraindication for pioglitazone. Pioglitazone and all other drugs of its class (Thiazolidinediones) are absolutely contraindicated in patients with heart failure.

Advantage- the Proactive study provided some data suggesting that people who used pioglitazone to optimize their treatment may have an advantage in terms of deaths, non-fatal heart attacks and strokes. Pioglitazone shows fewer incidences of cardiac disorders while comparing to rosiglitazone.

Disadvantage- It worsens the diabetic ketoacidosis &cardiac related problems.

Glibenclamide

Is a second generation Sulfonylurea, Sulfonylurea are a class of oral hypoglycemic agent that has been used for the treatment of type 2 diabetes for more than 50 years. They are described as insulin secretagogues and act on a set of receptors on the β-cell, thereby increasing insulin secretion. Currently, three agents are mostly available they are glibenclamide, glipizide, and glimepiride. The three drugs are fairly similar in action. There is some evidence that glipizide and glimepiride may be associated with less hypoglycemia than glibenclamide. Unlike the action of other classes of available insulin secretagogues, which are glucose dependent, sulfonlyureas are not. The sustained effect on the β -cell contributes both to the degree of efficacy and also to the rate of hypoglycemia seen with this class. Three drugs shows weight gain, in both cases as of mono & combination therapy with other classes of oral anti diabetic drug & with insulin (Hermann LS *et al.,* 1994, Lins PE *et al.,* 1988, Kahn SE *et al.,* 2006). In patients of glibenclamide gained 5.7 lb more than patients on nutrition therapy over a 10-year period. Increased and sustained insulin secretion, along with decreased glycosuria and increased hypoglycemia, are thought to fuel the weight gain seen with why this drug class. Sulfonylureas are not believed to have independent effects on adipose deposition or appetite.

Side effects- nausea, stomach pain, low fever, loss of appetite, presence of dark coloured urine, clay color stools, jaundice (yellowing of the skin or eyes),pale coloured skin, confusion & weakness, easy bruising with or without bleeding, purple or red pinpoint colored spots persistent sore throat or fever,

easy bleeding or bruising, stomach pain, yellow coloring of eyes & skin, dark urine, unusual tiredness or weakness, unusual or sudden weight gain, mood changes, hands or feet swelling , seizures.

Precaution- sulfonylurea may have ability to produce uncontrolled lowering of blood sugar below normal, so selection of patient & dosage and instructions are important to avoid hypoglycemic episodes. Hepatic or renal insufficiency leads to increased drug levels distribution of glyburide and the latter may also totally decrease gluconeogenic capacity of the body, both of which cause the increased risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with insufficiency of adrenal or pituitary glands , they have high chance to the hypoglycemic action of glucose-lowering drugs. Hypoglycemic condition may can't recognize properly especially in the elderly and in people under consumption of beta-adrenergic blocking regimens. Hypoglycemia is more likely to occur due to improper caloric consumption, after long time exercise, alcohol ingestion, or when under consumption of more than one glucose lowering drug. The risk of hypoglycemia may be increased with combination therapy. Loss of Control of Blood glucose when a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, surgery, may cause loss of control. At that times necessary to with draw glibenclamide (glyburide) and injection of insulin.

Drug interaction-hypoglycemia due to sulfonylureas may be increased by some other medication like non-steroidal anti-inflammatory drugs, and others like highly protein bound salicylates, chloramphenicol, sulfonamides,

probenecid, coumarins, MAO inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving glibenclamide (glyburide), the patient should be observed closely for hypoglycemia. If the patient is under consumption of such drugs are withdrawn from a patient receiving glibenclamide. Some drugs produce hyperglycemia and may lead to loss of control, such drugs like corticosteroids, thiazides and other diuretics, phenothiazines, estrogens, oral contraceptives, phenytoin, nicotinic acid, thyroid products, sympathomimetics, calcium channel blockers, and isoniazid(INH). When such drugs are administered to a patient receiving glibenclamide (glyburide), if anybody taking should be closely observed for loss of control. If the withdrawal of such drugs leads patient receiving glibenclamide (glyburide) cause glucose lowering effect (hypoglycemia).

There have a chance to interaction between glibenclamide to ciprofloxacin & oral miconazole ,

Contraindication- hypersensitivity & allergy, diabetic ketoacidosis, with or without coma, in such condition can overcome by insulin.

Advantages- it has a beneficiary action on cardiac action potential shape. It is highly economical as compared to vildagliptin.

Disadvantages- high chances of hypoglycemia, cardiac disfunctioning, chances of haemolytic anaemia

Acarbose

Acarbose is one of the anti-diabetic drug used to treat type 2 diabetes mellitus and, in some countries used for prediabetes condition also, Alpha-glucosidase inhibitors (AGIs;acarbose, miglitol, voglibose) are widely used in the treatment of patients with type 2 diabetes but not more prefer in single therapy. Alpha-glucosidase inhibitors delay the absorption of carbohydrates from the small intestine and thus have a lowering effect on postprandial blood glucose and insulin levels.

Acarbose inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates, to be specific, alpha-glucosidase are a type of enzymes present in the small intestinal brush border and pancreatic alpha-amylase. The enzyme pancreatic alpha-amylase will hydrolyzes complex starches to oligosaccharides at the small intestinal lumen, in this membrane-bound intestinal alpha-glucosidase enzyme will hydrolyze oligosaccharides , trisaccharides, and disaccharides to glucose & other monosaccharides in the small intestine. The inhibition of these enzymes will reduce the rate of digestion of complex carbohydrates to simple one. So less glucose is absorbed, due to carbohydrates are not broken down into small glucose molecules. So the short-term effect of these drugs is to decrease current blood glucose levels; the long-term effect will cause the reduction in Hb_{A1c} level (Rutten et al.,). This reduction leads to absolute decrease of Hb_{A1c} values in diabetic patients.

Side effect- nausea , stomach pain, loss of appetite, dark urine, clay-colored stools.

Jaundice (yellowing of the skin or eyes).Less serious side effects may include mild stomach pain, gas, bloating, diarrhea, low fever

Precaution-This medication should not be used if you have certain medical conditions. Before using this medicine, consult your doctor or pharmacist if you have: very high blood sugar levels (diabetic ketoacidosis), severe liver disease (cirrhosis), and intestine/bowel problems (e.g., inflammatory bowel disease, intestinal blockage/ulcers, and digestion/absorption disorders).

Drug interaction- certain drugs tend to produce hyperglycemia and may lead to loss of glucose control. It includes corticosteroids, thiazide & other diuretics, estrogens, oral contraceptives, thyroid products, phenytoin, nicotinic acid, sympathomimetics, calcium channel-blockers, and INH. If the patient under consumption with such drugs is administered to a patient receiving acarbose, should be closely observed because there is a chance of loss of blood glucose control, when ever withdrawn such drugs then recommend the patient to take acarbose in combination with sulfonylureas or insulin & patients should be observed closely for hypoglycemia.

Patients under consumption of insulin may leads to hypoglycemic condition. Acarbose as combination with sulfonylurea or insulin may also leads to further lowering of blood glucose. If hypoglycemia occurs, appropriate adjustments in the dosage of these agents should be done. Very rare chances of hypoglycemic shock have been reported in patients receiving acarbose therapy in combination with sulfonylureas and/or insulin.

Intestinal adsorbents like charcoal and digestive enzyme preparations containing carbohydrate-splitting enzymes like amylase, and pancreatin may decrease the effect of acarbose, so avoid concomitant consumption of both.

Acarbose have ability to change the bioavailability of digoxin when it co-administered, in this may require digoxin dose adjustment.

Contraindication-it is contraindicated in patients with hypersensitivity reaction, & it is contraindicated in patients with diabetic ketoacidosis & cirrhosis. And also contra- indicated in patients with IBD (inflammatory bowel disease), partial intestinal obstruction, colonic ulceration, or in patients predisposed to intestinal obstruction. And patients who have chronic intestinal diseases associated with digestion or absorption.

Combination therapy

The major combination therapy of vildagliptin is with metformin& pioglitazone are widely preferred now a days, its combined action is more beneficiary as well as less side effect comparatively with their individual therapy. Combined action of vildagliptin with metformin produce improved glycemic control .Vildagliptin works by increasing the amount of two body incretin hormones, like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), these hormones are normally produced naturally by the body with respect to food consumption. The hormone's function is to control(maintain as normal)blood sugar level. Primarily, they stimulate the pancreas to produce insulin in response to increasing levels of glucose in the blood and metformin improves

hyperglycemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). Metformin activates AMP-activated protein kinase (AMPK), an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats; activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. In the combination therapy of vildagliptin with pioglitazone was improved incretin hormones production as well as increased cell sensitivity to insulin, including activation of peroxisome proliferators activated receptor and alteration of hepatic glucose metabolism, and promote glucose utilization in peripheral tissues.

Side effects-its side effects may vary with individual people in different ways. The major known side effects associated with this medicine are

- Headache (when used with metformin or a sulphonylurea).
- Dizziness (with metformin or a sulphonylurea).
- Low blood sugar levels (with metformin or a sulphonylurea).
- Nausea (with metformin).
- Feeling weak (with a sulphonylurea).
- Weight gain (with a glitazone).
- Swelling of the legs and ankles due to excess fluid retention (with a glitazone).
- Tremor (when used with metformin or a sulphonylurea).

Precaution-never use with patients having type 1 diabetes ,diabetic ketoacidosis, Do not use in patients having hepatic impairment, including patients have pre-treatment ALT or AST > 3x ULN. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue it.

Advantage- DPP-4 inhibitors appear to be extraordinarily well tolerated with metformin & Pioglitazone.

Disadvantages- it is not economical compare to other oral anti hypoglycemic agent.

LITERATURE REVIEW

Stephen aronoff *et al.*, 2000, conducted a study of pioglitazone monotherapy treatment in type 2 diabetes; the objective of the study is to evaluate the efficacy and safety of four doses of pioglitazone monotherapy in the treatment of patients with type 2 diabetes. There were 408 patients randomized in this multicenter double-blind placebo-controlled clinical trial. Patients who had HbA1c_7.0%, fasting plasma glucose (FPG) 140 mg/dl, and C-peptide 1 ng/ml were randomized to receive placebo or 7.5, 15, 30, or 45 mg pioglitazone administered once a day for 26 weeks. Patients treated with 15, 30, or 45 mg pioglitazone had significant mean decreases in HbA1c and FPG. In the 15, 30, or 45-mg pioglitazone groups, there were significant mean percent decreases in triglycerides, significant mean percent increases in HDL cholesterol,and only small percent changes in total cholesterol and LDL. The subset of patients naive to therapy had greater improvements in HbA1c and FPG compared with previously treated patients. The overall adverse event profile of pioglitazone was similar to that of placebo.

Phillips *et al.*, 2003, conducted the study of glycemic control of Acarbose in over weight patient having type 2 Diabetes, objective of the study to investigate the efficacy and safety of acarbose as add-on therapy in overweight type 2 patients with diabetes inadequately controlled by metformin. And it conducted a multicenter, randomized, double-blind, placebo-controlled, parallel group design. After a 4-week placebo run-in period, subjects were randomized to either acarbose (titrated up to 100 mg b.i.d.) or placebo. The primary efficacy variable was the change in HbA1c from baseline to the end of the 24-week treatment period. Change in fasting blood glucose

was assessed as a secondary efficacy parameter. And they concluded the analysis from baseline to week 24 (81 patients for HbA1c and 82 for fasting blood glucose) showed statistically significant differences between acarbose and placebo treatment in HbA1c and fasting blood glucose. 18 patients (47%) in the acarbose group were classified as responders with a 5% reduction in HbA1c (relative to baseline) at the end point compared to 6 (14%) in the placebo group. The safety profiles were similar for both treatment groups except for the higher incidence of gastrointestinal side effects during acarbose therapy.

Schernthaner *et al.*, 2004, conducted a study on efficacy and safety of Pioglitazone Vs Metformin in patients with Type 2 Diabetes mellitus. This study compared metabolic control in drug-naive type 2 diabetes patients given either pioglitazone or metformin. Eleven hundred and ninety-nine patients with poorly controlled type 2 diabetes mellitus (HbA1c), 7.5–11%; were randomized to receive either pioglitazone (<45 mg/d) or metformin (<850 mg, three times daily). HbA1c, fasting plasma glucose (FPG), insulin levels, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol, triglycerides, free fatty acids, and urinary albumin/creatinine ratio were measured. The assessed result were Mean HbA1c decreased in both treatment groups from baseline to wk 52 (1.4% and1.5%). Significantly greater mean reductions in FPG were observed in the pioglitazone group than in the metformin group (*P*_ 0.016). Favourable changes in triglycerides and HDL-C were more pronounced with pioglitazone.

Smith *et al.*, 2004, conducted a study on Rosiglitazone, But Not Glyburide, Reduces Circulating Proinsulin and the Proinsulin: Insulin Ratio in Type2 Diabetes. Objective of the studies was to assess the effects of the thiazolidinedione insulin sensitizer, rosiglitazone, on indirect markers of cell function and cardiovascular risk in people with type 2 diabetes by measuring plasma PI and the PI : IRI ratio. Type 2 diabetes patients enrolled in two randomized double-blind studies comparing the effects of rosiglitazone (4 or 8 mg/d) with placebo (study 1, 26-wk treatment)or the sulfonylurea glyburide (study 2, 52-wk treatment).Treatment with rosiglitazone for 26 wk (study 1)produced significant dose-dependent decreases in both plasma PI concentrations (18–29%) and the PI:IRI ratio compared with baseline (7–14%) and placebo (19–29%) ($P < 0.001$).A significant increase in the PI: IRI ratio in placebo-treated patients occurred ($P < 0.001$). In study 2, rosiglitazone also significantly reduced both plasma PI and the PI: IRI ratio compared with baseline ($P < 0.001$). In contrast, glyburide significantly increased both plasma PI (45%; $P < 0.001$) and the PI: IRI ratio (10%) ($P < 0.05$ *vs.* baseline). These results show that rosiglitazone and glyburide have differential effects on absolute PI levels and the PI: IRI ratio in people with type 2 diabetes.

C.Pan *et al.*, 2007, conducted a comparative study of Vildagliptin Vs Acarbose monotherapy in type 2 diabetic patients, the aim of the study to compare the efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor, vildagliptin, with the alpha glucosidase inhibitor, acarbose, in drug-naive patients with Type 2 diabetes. multi-centre, randomized, double-blind, parallel-arm study compared the efficacy and tolerability of vildagliptin (100 mg daily, given as 50 mg twice daily,*n*= 441) and

acarbose (up to 300 mg daily, given as three equally divided doses,*n*= 220) during 24-week treatment. The assessed result where Monotherapy with vildagliptin or acarbose decreased HbA1c to a similar extent during 24-week treatment. The

decrease in fasting plasma glucose was similar with acarbose and vildagliptin .Body weight did not change in vildagliptin-treated patients but decreased in acarbose-treated patient.The proportion of patients experiencing any adverse event (AE) was 35% vs. 51% in patients receiving vildagliptin or acarbose, respectively; gastrointestinal AEs were significantly more frequent with acarbose (25.5%) than vildagliptin (12.3%). No hypoglycaemia was reported for either group.

Julio rosenstock *et al.*, 2008, conducted study on effects of the Dipeptidyl Peptidase-IV Inhibitor Vildagliptin on Incretin Hormones, Islet Function, and Postprandial Glycemia, the objective of the study to determine the effects of vildagliptin on incretin hormone levels, islet function, and postprandial glucose control in subjects with impaired glucose tolerance (IGT).2-week, double-blind, randomized, parallel-group study comparing vildagliptin (50 mg q.d.) and placebo was conducted in 179 subjects with IGT (2-h glucose 9.1 mmol/l, A1C 5.9%). Plasma levels of intact glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), glucose, insulin, C-peptide, and glucagon were measured during standard meal tests performed at baseline and at week 12.study assessed by ANCOVA method vildagliptin increased GLP-1 and GIP and decreased glucagon. Although postprandial insulin levels were unaffected, prandial glucose excursions were reduced, representing an_30% decrease relative to placebo.

D'alessio *et al*., 2008, conducted study on Treatment with the Dipeptidyl Peptidase-4 Inhibitor Vildagliptin Improves Fasting Islet-Cell Function in Subjects with Type 2 Diabetes; the objective of the study was to examine the effects of DPP-4 inhibition on fasting islet function. It's a randomized, double-blind, placebo-controlled trial. Conducted on a Fourty-one subjects withT2DM were treated with metformin or diet, having good glycemic control with Glycosylated haemoglobin values of 6.2–7.5%. Subjects were treated with vildagliptin (50 mg twice daily) or placebo for 3 months, followed by a 2-wk washout .and measured insulin secretion in response to iv glucose and arginine before and after treatment and after drug washout. small and comparable reductions in glycosylated haemoglobin in both groups over 3 months. Vildagliptin increased fasting GLP-1 levels in subjects taking metformin, but not those managed with diet, and raised active GIP levels slightly. DPP-4 inhibitor treatment improved the acute insulin and C-peptide responses to glucose (50 and 100% respectively; *P* 0.05) and increased the slope of the C-peptide response to glucose (33%; *P* 0.023). DPP-4 inhibition has metabolic benefits in addition to enhancing meal-induced GLP-1 and GIP activity.

Bo ahrén, 2008, Department of Clinical Sciences, Division of Medicine, Lund University, run a study on combination therapy of DPP4 inhibitor Vildagliptin and Metformin in type 2 diabetic patients, clinical experience with DPP-4 inhibition is based on vildagliptin (GalvusR, Novartis) and sitagliptin (JanuviaR, Merck) where assessed during a 52 weeks combination versus continuous therapy with metformin alone . Both have also been shown to efficiently improve glycemic control when added to ongoing metformin therapy in patients with inadequate glycemic control.

They reduce HbA1c levels by 0.65%–1.1% (baseline HbA1c 7.2–8.7%). The combination of DPP-4 inhibition and metformin has been shown to be highly tolerable with very low risk of hypoglycemia. Hence, DPP-4 inhibition in combination with metformin is an efficient, safe and tolerable combination therapy for type 2 diabetes.

Mikhai, 2008 conducted the study on combination therapy with DPP4 inhibitors and Pioglitazone in type 2 diabetis. The objective of this study is to critically evaluate sitagliptin and vildagliptin in combination with pioglitazone. The result was to be vildagliptin to ongoing pioglitazone therapy is associated with reduction in average hemoglobin A1C (HbA1c) levels of approximately 0.7% compared with placebo and 1% compared with baseline after 24 weeks. When started concomitantly in drug-naïve patients, the combination of pioglitazone 30 mg and vildagliptin 100 mg qd reduces HbA1c by 1.9% after 24 weeks, compared with 1.1% with pioglitazone monotherapy. In general, the addition of DPP-4 inhibitors to pioglitazone was well tolerated, did not increase the incidence of hypoglycaemia, and did not substantially worsen the weight-gain induced by pioglitazone. The combination of sitagliptin or vildagliptin with pioglitazone can be a useful therapeutic approach in patients with type 2 diabetes who cannot tolerate metformin or a sulfonylurea.

Mathieu & Degrande, 2008, conducted study on vildagliptin: a new oral treatment for type 2diabetes mellitus. Vildagliptin involving approximately 22,000 patients and 7000 patient-years of exposure to vildagliptin has shown that the agent is well tolerated and efficacious in improving glycemic control in patients with type 2

diabetes mellitus (T2DM). Monotherapy trials have shown that significant HbA1c lowering is accompanied by body weight-neutral and lipid-neutral effects, low risk of oedema, and low risk of hypoglycemia.These characteristics make vildagliptin a favourable partner for combination therapy. Studies of vildagliptin as an add-on to metformin have shown significant improvements in glycemic control (comparable to that of thiazolidinedione add-on), with the combination being well tolerated and associated with low risks for hypoglycemia and adverse effects on weight or lipid levels.

Ahr´en *et al.*, 2010, studied Changes in Prandial Glucagon Levels After a 2-Year Treatment With Vildagliptin or Glimepiride in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy, objective of the study to determine if the dipeptidyl peptidase-4 inhibitor vildagliptin more effectively inhibits glucagon levels than the sulfonylurea glimepiride during a meal. Glucagon responses to a standard meal were measured at baseline and study end point (mean 1.8 years) in a trial evaluating add-on therapy to metformin with 50 mg vildagliptin b.i.d. compared with glimepiride up to 6 mg q.d. in type 2 diabetes (baseline A1C 7.3 ± 0.6%). A1C and prandial glucose area under the curve (AUC) 0–2 h were reduced similarly in both groups, whereas prandial insulin AUC 0–2 h increased to a greater extent by glimepiride. Prandial glucagon AUC 0–2h decreased by vildagliptin (*n* 137) and increased by glimepiride (*n* 121). The between-group difference was 7.3 ± 2.1 mol . Vildagliptin therapy but not glimepiride improves postprandial cell function, which persists for at least 2 years.

Schweizer *et al*., 2011, conducted a study to assess the general safety & tolerability of Vildagliptin in type 2 diabetic patients. The aim of this study is therefore to assess the general safety and tolerability, including incidences of the most common adverse events (AEs).The study conducted by 38 studies of ≥12 to ≥104 weeks' duration. AE profiles of vildagliptin (50 mg bid; N = 6116) were evaluated relative to a pool of comparators (placebo and active comparators; N = 6210). Absolute incidence rates were calculated for all AEs, serious AEs (SAEs), Discontinuations due to AEs, and deaths. The results was to be Overall AEs, SAEs, discontinuations due to AEs, and deaths were all reported with a similar frequency in patients receiving vildagliptin (69.1%, 8.9%, 5.7%, and 0.4%, respectively)and patients receiving comparators (69.0%, 9.0%, 6.4%, and 0.4%, respectively), whereas drug related AEs were seen with a lower frequency in vildagliptin-treated patients (15.7% vs. 21.7% with comparators). The incidences of the most commonly reported specific AEs were also similar between vildagliptin and comparators, except for increased incidences of hypoglycaemia, tremor, and hyperhidrosis in the comparator group related to the use of sulfonylurea.

AIM AND OBJECTIVE

Aim

To compare the efficacy & safety of DPP4 inhibitor Vildagliptin with or without Biguanide derivative Metformin, Alfa glucosidase inhibitor acarbose, Sulfonylurea derivative Glibenclamide, Thiazolidinedione derivative Pioglitazone & DPP4 inhibitor Vildagliptin with Thiazolidinedione derivative Pioglitazone.

Objective

- Compare the efficacy & safety of DPP4 inhibitor Vildagliptin with or without Biguanide derivative Metformin to Alfa glucosidase inhibitor acarbose.

- Compare the efficacy & safety of DPP4 inhibitor Vildagliptin with or without Biguanide derivative Metformin to Sulfonylurea derivative Glibenclamide.

- Compare the efficacy & safety of DPP4 inhibitor Vildagliptin with or without Biguanide derivative Metformin to Thiazolidinedione derivative Pioglitazone.

- Compare the efficacy & safety of DPP4 inhibitor Vildagliptin with or without Biguanide derivative Metformin to DPP4 inhibitor Vildagliptin with Thiazolidinedione derivative Pioglitazone.

PLAN OF WORK

This is designed in three different phases to achieve the objectives.

PHASE 1

- Initial study to identify the scope of work.
- Literature survey.
- Preparation of study protocol.

PHASE 2

- Gaining consent from hospital authority.
- Designing of data entry format.

Based on the topic articles were collected. From the different articles prepare the interview questionnaire form with the help of standard references. Prepared questionnaire was discussed with guide.

- Data collection.

PHASE 3

- Analysis of data

  All data's were coded, entered, and analyzed using Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta.

- Report and submission.

MATERIALS AND METHODS

Study design

This is a prospective observational study (one in which the data to be studied are yet to be generated, the events having not yet occurred.)

Study site

This study was conducted in Dialife diabetic & obese centre Manjeri - Kerala, is a hundred bed hospital, specially designed for diabetic and associated diseases like diabetic neuropathy (foot ulcer) & retinopathy.

Duration of study

Present prospective study was carried out in between June 2011 to March 2012.

Study population

Total number of population is two hundred and eighty (280) from that two hundred and seven (207) patients are selected & seventy three patients had dropped due to irregular follow up.

Study criteria

Inclusion criteria

- Age category-30 to 8o.
- The patients who have HbA1c range in between 5 to 10.
- Patients those are taking only oral anti diabetic agents.
- The patients those have normal or near normal AST & ALT values.

Exclusion criteria

- Patients those under insulin injection.
- Patients with life threatening diseases like Angina pectoris, CAD etc.
- Patients with foot ulcer.
- Patient with gestational diabetis.
- Patients with type 1 Diabetis.

Sources of data

- Direct observational & questionnaire method.
- Lab report collection.
- Patients prescription

Method of data collection

- By this study demographical data's were collected by using questionnaire form with proper personal interview to the patients, in this demographical data's included as follows age, sex, BMI, Educational Qualification, social history and Family history. Other data's like symptoms, co-morbidity, drug category also included.
- On the first visit onwards we starting the procedure, as per the proforma collect all the data like demographic, lab data like efficacy & safety profile.
- Collect blood sample for following tests FBS, RBS, HbA1c, lipid & hepatic safety profile by lab technician. The same procedures continue on 2^{nd}& 3^{rd} visit. But not conducting HbA1c test in second visit.

RESULT & DISCUSSION

All together two hundred and seven (207) patients were enrolled in to the study over a period of 10 months from department of diabetes, dialife diabetic & obese centre Manjeri.

DEMOGRAPHIC DATA:-

Sex & Age wise Distribution (n=207):-

Of the two hundred and seven (207) patients examined, In that males 133 (64.25%) and females 74 (35.74%). The total patients are classified in to two groups based on the number of drug consumption (Monotherapy & Combination therapy) in monotherapy group males 86(64.7%) & females 47(35.3%) are there out of 133,in combination therapy consist of 74 patients in that 47(63.3%) males & 27 females(36.5%). The mono & combination therapy again sub divided in to six on the basis of drug prescribed. The sex wise distribution from each group more males 30 (75 %) out of 40 is in vildagliptin + metformin group, more females 18 (38.6 %) out of 47 in glibenclamide group.

In age wise distribution two hundred and seven (207) patients are divided in to five age groups. They are 35-45 year, 46-55 year, 56-65 years, 66-75 years, and 76-85 years. In that more patients 67 (32.36%) are in age group of 46-55 years & 56-65 years in each group. Study of Muralikrishnan R *et al*., 2001 also shows the prevalence of diabetic in age group of 50 and above, The least number of patients 4 (1.93%) are present in 76-85 year age group.

Table .1 Age & Sex wise distribution of patient

Parameters		Monotherapy therapy								Combination therapy			
		vildagliptin		Pioglitazone		Glibenclamide		Acarbose		Vildagliptin+ Metformin		Vildagliptin+ Pioglitazone	
Total patients 207	No	**34**		**39**		**47**		**13**		**40**		**34**	
	%	**16.42**		**18.84**		**22.72**		**6.28**		**19.32**		**16.42**	
Male-133 Female-74		No	%	No	%	No	%	No	%	No	%	No	%
Sex	Male	21	61.76	25	64.1	29	61.7	10	76.92	30	75	18	52.94
	Female	13	38.24	14	35.9	18	38.6	3	29.08	10	25	16	47.06
Age In years	35-45	4	11.76	15	38.46	15	31.91	6	46.15	6	15	2	5.88
	46-55	15	44.12	12	30.77	19	40.43	Nil	0	14	35	7	20.59
	56-65	14	41.18	10	25.64	11	23.4	4	30.77	14	35	14	41.18
	66-75	1	2.94	2	5.13	1	2.13	3	23.08	5	12.5	9	26.47
	76-85	Nil	0	Nil	0	1	2.13	Nil	0	1	2.5	2	5.88

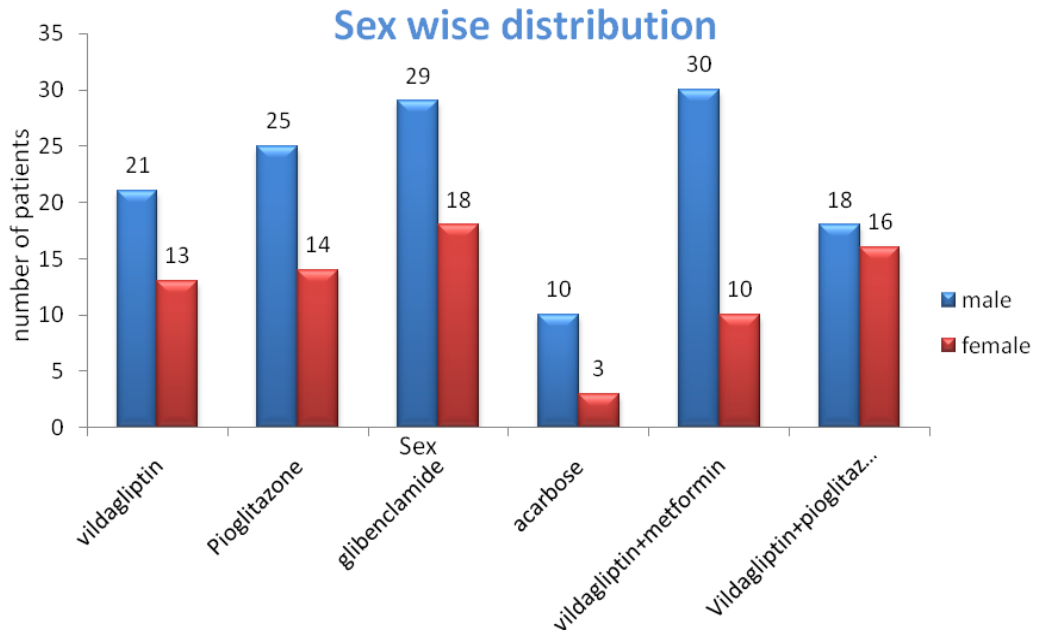


Figure.1a Sex wise distribution of patients

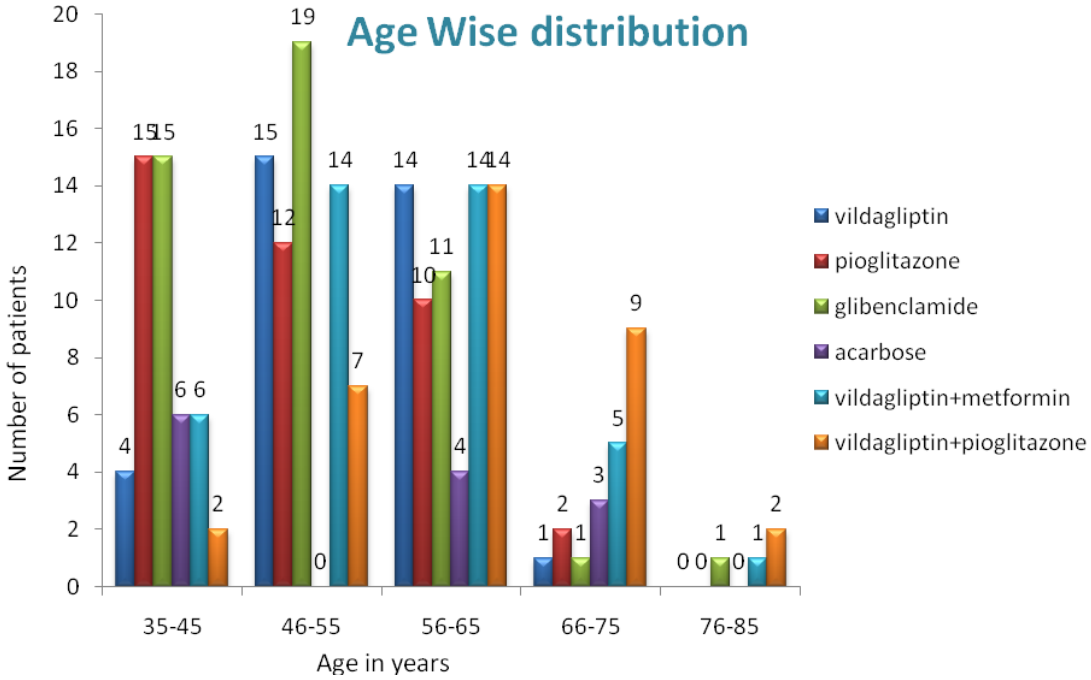


Figure.1b Age wise distribution of patients

Family history & duration of therapy report (n=207):-

Among the study population 176 (85.02%) have family history of diabetes mellitus & 31(14.97%) doesn't with family history. According to American Diabetes Association (ADA) Type 2 diabetes has a stronger link to family history and lineage than type 1, although it too depends on environmental factors. Studies of twins have shown that genetics play a very strong role in the development of type 2 diabetes. Lifestyle also influences the development of type 2 diabetes. In drug wise family history as follows, the patients with vildagliptin 30 (88.2%)have family history and 4 (11.7%) doesn't have family history, in pioglitazone group 32 (82%) have family history and 7 (17.9%) doesn't have, in glibenclamide group 37(78.72%) have family history and 10(21.28%) doesn't have, in acarbose group 10 (76.9%) have history and 3(29%) doesn't have, in vildagliptin+metformin combination group 37 (92.5%) have family history 3 (7.5%) doesn't have family history, in vildagliptin+pioglitazone group 30(88.2%) have family history of diabetes mellitus and 4 (11.7%) haven't family history of diabetes mellitus. The details of family history of diabetes mellitus patients are presented in Table 2 and Figure 2a.

In the study population, 34 patients (16.42%) had a treatment history of less than 1 year, followed by 1-5 year in 71 patients (34.29%), followed by 5-10 years in 70 patients (33.81%), followed by >10 years in 32 patients (15.45%), The details of duration of therapy type of 2 diabetes mellitus are presented in Table 2 and Figure 2b.

Table 2 Duration of therapy & Family history report

Parameters		Monotherapy								Combination therapy			
		Vildagliptin		Pioglitazone		Glibenclamide		Acarbose		Vildagliptin+ Metformin		Vildagliptin+ Pioglitazone	
		No	%	N0	%	No	%	No	%	No	%	No	%
Duration of Therapy (in years)	< 1	Nil	0	14	35.9	14	29.79	4	30.7	2	5	Nil	0
	1-5	2	5.8	21	53.8	28	59.58	7	53.9	10	25	3	8.82
	5-10	24	70.5	3	7.7	2	4.26	1	7.69	18	45	22	64.8
	>10	8	23.5	1	2.56	3	6.38	1	7.69	10	25	9	26.5
Family history	Yes	30	88.2	32	82.	37	78.72	10	76.9	37	92.5	30	88.2
	No	4	11.7	7	17.9	10	21.28	3	29.0	3	7.5	4	11.7

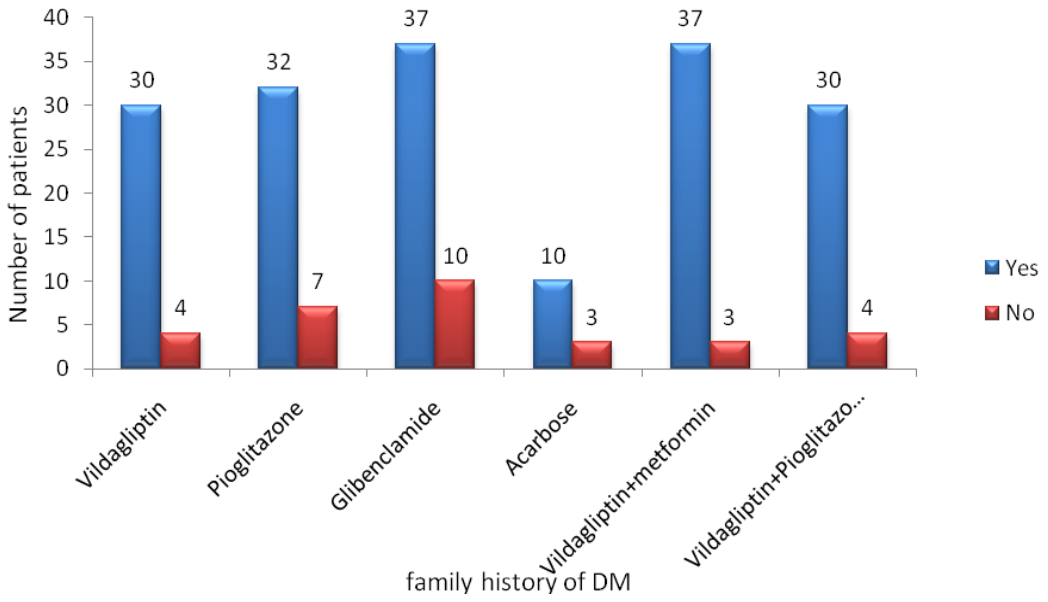


Figure.2a Diabetic related Family history of patient

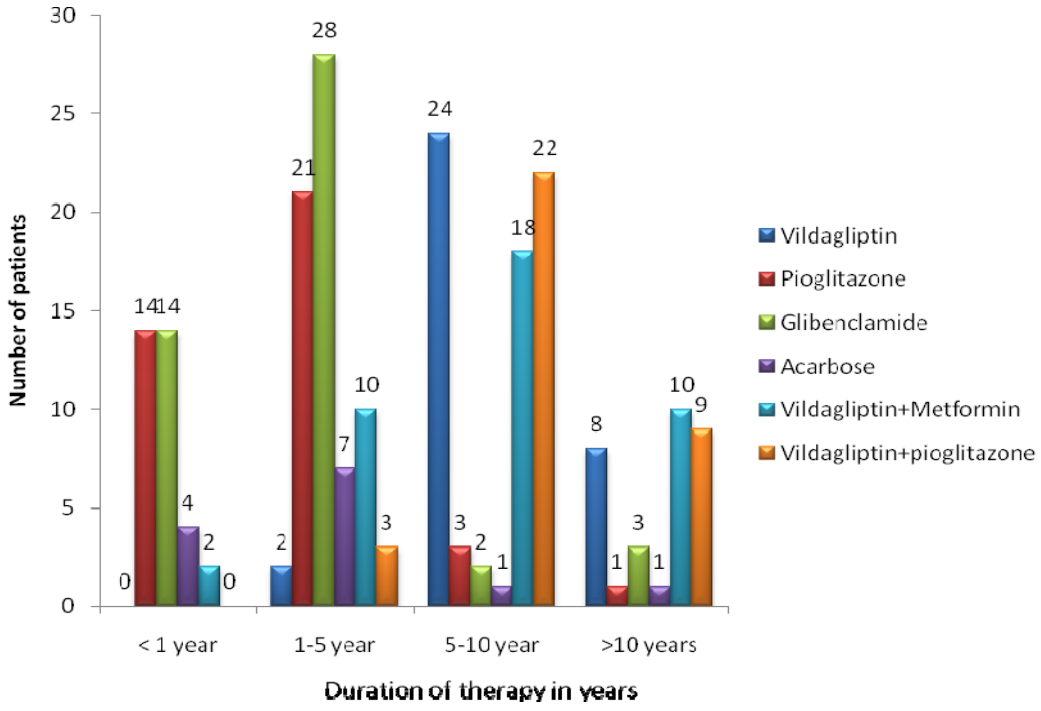


Figure.2b Duration of therapy

Body Mass Index (BMI) result:-

Body mass index of two hundred and seven patients (207) was observed and marked in initial& final therapy period that data is mentioned in the Table-3& Figure 3, in that we can assess the pre, post & their changes of the BMI in (mean ± SD).

Table 3-Body mass index wise distribution of patients

Group	Body mass index(BMI)			P value
	Initial therapy	**Final therapy**	**Change in BMI**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Monotherapy				
Vildagliptin	25.49 ± 2.29	24.73 ± 2.39	0.24±0.52	
Glibenclamide	25.24 ± 2.45	25.4 ± 2.44	-0.16±0.43	
Pioglitazone	25.74 ± 2.69	25.96 ± 2.6	-0.22±0.43	
Acarbose	26.81 ± 3.45	27.06 ± 3.44	-0.25±0.39	0.0001 Significant
Combination therapy				
Vildagliptin + Pioglitazone	25.32 ± 2.29	25.56 ± 2.29	-0.24±0.32	
Vildagliptin +Metformin	27.43 ± 2.93	27.02 ± 2.8	0.41 ± 0.53	

In the monotherapy group the acarbose group patients pre treatment BMI (26.81 ± 3.45) & post treatment BMI (27.06 ± 3.44) are higher than that of other groups & also it showing higher negative weight decrease (weight gain) (-0.25 ± 0.39). Study of *Delgado H et.al, 2002* shows Variable effects on weight have been seen with acarbose, Vildagliptin group patients pretreatment BMI (25.49 ±2.29) is more than that of Glibenclamide (25.24 ± 2.45) group, but post treatment BMI of

vildagliptin (24.73 ±2.39) is lesser than that of Glibenclamide (25.4 ±2.44) and also the vildagliptin group only shows positive weight (0.24 ± 0.52) decrease. Pioglitazone group also shows a negative weight decrease (-0.22±0.43) Richard e Pratley *et al.*, study also shows the same effect of thiazolidinediones (pioglitazone). In combination therapy Vildagliptin + Metformin group (0.41 ± 0.53) showing greater decline of body weight than Vildagliptin+ Pioglitazone (-0.24 ± 0.32) group.

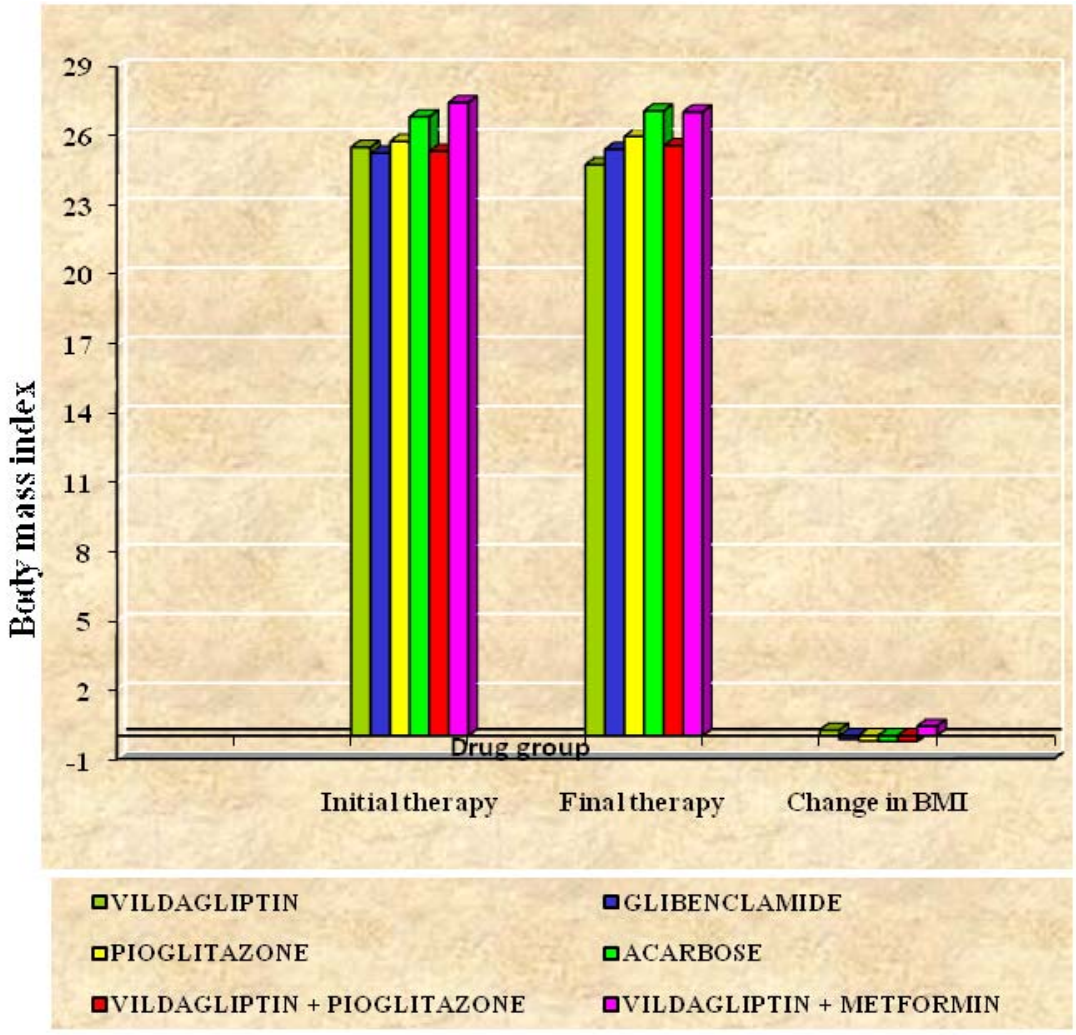


Figure.3 Body mass index chart

Fasting blood sugar (FBS) level in diabetic patients:-

Fasting blood sugar of two hundred and seven (207) patients was observed and marked in pre& post treatment period that data is mentioned in the Table-4& Figure 4, in that we can assess the pre, post & their changes of the BMI in (mean ± SD).

Table 4-Fasting blood sugar distribution in diabetic patients

Group	Fasting blood sugar(FBS)			P value
	Pre treatment	Post treatment	Change in FBS	
	Mean ± SD	Mean ± SD	Mean ± SD	
Monotherapy				
Vildagliptin	142.6 ± 36.0	107.6 ± 23.7	35.0 ± 22.8	
Glibenclamide	135.4 ± 33.2	119.2 ± 43.4	16.2 ± 31.7	
Pioglitazone	130.4 ± 36.3	116.5 ± 28.3	13.9 ± 24.4	0.0001
Acarbose	151.1 ± 34.5	161.2 ± 39.1	-10.1 ± 32.6	Significant
Combination therapy				
Vildagliptin + Pioglitazone	139.1 ± 29.7	107.4 ± 33.4	31.8 ± 47.4	
Vildagliptin + Metformin	161.1 ± 48.5	124.6 ± 31.8	36.5 ± 27.6	

In that monotherapy group vildagliptin pre-treatment mean value (142.6±36.0) is greater than that of other group but its post-treatment day value (107.6 ± 23.7) is lesser than that of the pre-treatment day value of other group live glibenclamide, pioglitazone & acarbose. And also it shows a high mean decrease range (35.0 ± 22.8) than other groups. Harvey *et al.,* study shows the vildagliptin has better effect & increased incretin hormone than Pioglitazone. *Mathieu and Degrande* Studies shows

a better decrease of fasting blood sugar without inducing hypoglycemia. The acarbose monotherapy post-treatment day mean value (161.2 ± 39.1) is more than that of pre-treatment day mean value (151.1 ± 34.5), that means it shows a less control or negative decrease of fasting blood sugar (-10.1 ± 32.6) level. In combination therapy group vildagliptin+metformin combination showing a pre &post treatment day FBS values of 161.1 ± 48.5, 116.6 ± 33.5, that means it shows a better mean FBS reduction (36.5 ± 27.6) than that of vildagliptin+pioglitazone group (31.8 ± 47.4).In both (mono & combination) group comparison also vildagliptin+metformin combination (36.5 ± 27.6) shows better decrease than that of vildagliptin alone & vildagliptin+pioglitazone combination. And shows a significant P (0.0001) value decrease.

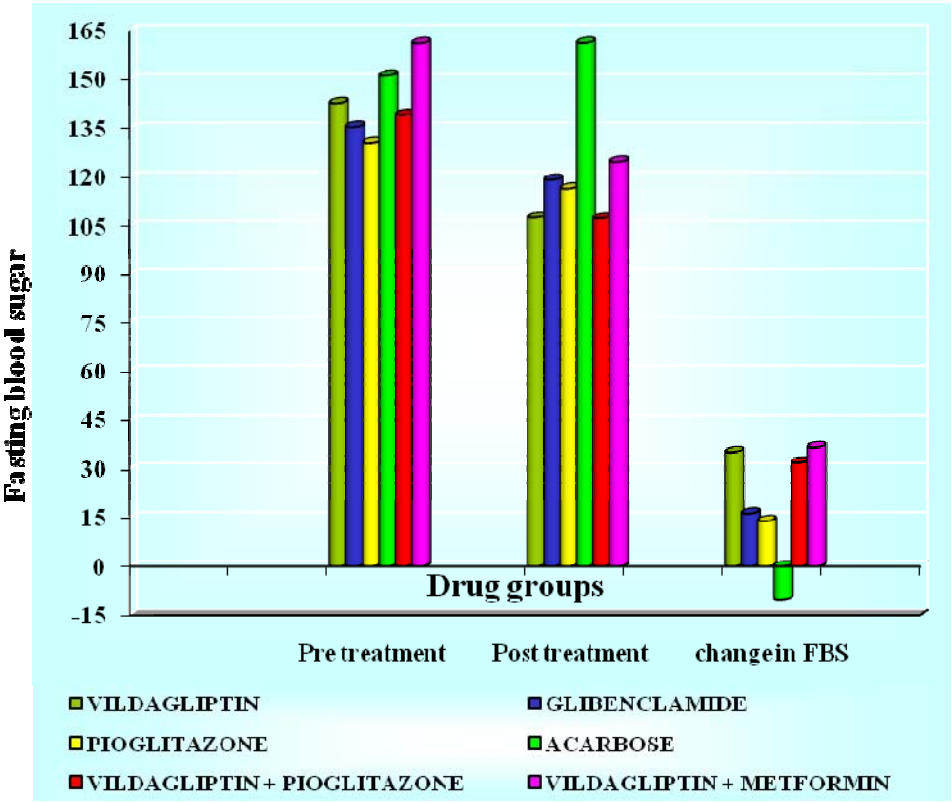


Figure. 4 Fasting blood sugar level

Random blood sugar (RBS) level data:-

Random blood sugar of two hundred and seven (207) was observed and marked in pre& post therapy period that data is mentioned in the Table-5 & Figure 5, in that we can assess the pre, post & their changes of the BMI in (mean ± SD).

Table.5 Random blood sugar level

Group	Random blood sugar(RBS)			P value
	Pre treatment	Post treatment	Mean Decrease	
	Mean ± SD	Mean ± SD	Mean ± SD	
Monotherapy				0.0001 Significant
Vildagliptin	219.4 ± 53.0	170.4 ± 30.6	79.1 ± 42.2	
Glibenclamide	227.4 ± 61.0	177 ± 56.2	50.4 ± 49.4	
Pioglitazone	225.4 ± 52.3	188 ± 42	37.5 ± 45.6	
Acarbose	254.1 ± 61.1	236.2 ± 53.2	17.8 ± 61.4	
Combination therapy				
Vildagliptin + Pioglitazone	241.5 ± 43.5	182.8 ± 54.3	58.7 ± 74.4	
Vildagliptin + Metformin	281.3 ± 56.5	196.4 ± 36.4	85 ± 47.2	

In that monotherapy group vildagliptin pre-treatment mean value (219.4 ± 53.0) is greater than that of other group but its post-treatment day value (170.4 ± 30.6) is lesser than that of the pre treatment day value of other group live glibenclamide, pioglitazone & acarbose. And also it shows a high mean decrease range (35.0 ± 22.8) than other groups. Its mean RBS decreasing rate (79.1 ± 42.2) is twice of pioglitazone

(37.5 ± 45.6) group & four and half time more than that of acarbose (17.8 ± 61.4) acarbose group. According to *sanjay karla 2010,* vildagliptin have better effect than sulfonyl urea, thiozolidindiones & α-glucosidase inhibitors. In combination therapy group vildagliptin+metformin shows a better mean RBS reduction (85 ± 47.2) than that of vildagliptin+pioglitazone group (58.7 ± 74.4). In both (mono & combination) group comparison also vildagliptin +metformin combination (85 ± 47.2) shows better decrease than that of vildagliptin alone & vildagliptin +pioglitazone combination. And shows a significant P (0.0001) value decrease

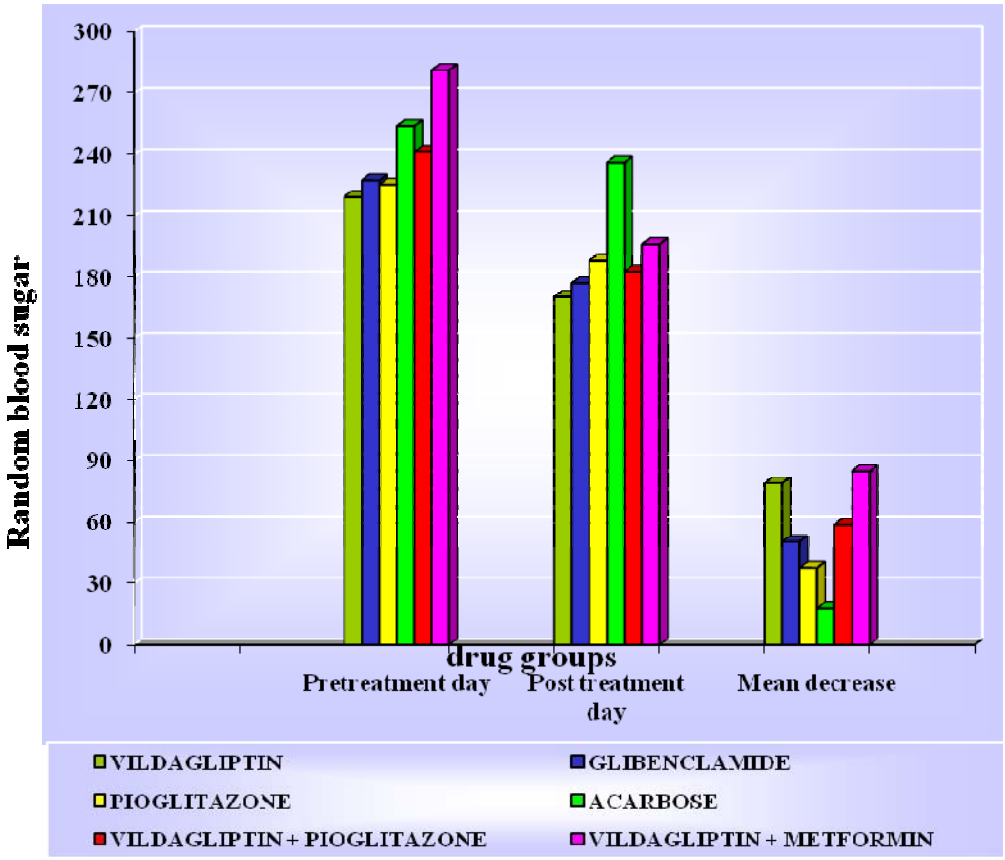


Figure .5 Random blood sugar graph

Glycosylated haemoglobin level data (HbA1c):-

HbA1c of 207 patients observed and recorded the values of first (pre-treatment day) visit and third (Post-treatment day). Data is mentioned in the Table-6 & Figure 6, in that we get the pre, post & their changes of the HbA1c in (mean ± SD) values. In the monotherapy group the vildagliptin group has higher value of pre-treatment HbA1c (7.81 ± 0.61) than that of other groups, from this we can understand vildagliptin is highly preferable in higher range blood glucose level.

Table.6 Glycosilated heamoglobin data

Group	Glycosilated heamoglobin(HbA1c)			P value
	Pre-treatment	Post-treatment	Change in HbA1c	
	Mean ± SD	Mean ± SD	Mean ± SD	
Monotherapy				0.0001 Significant
Vildagliptin	7.81 ± 0.61	7.31 ± 0.62	0.5 ± 0.35	
Glibenclamide	7.37 ± 0.82	7.07 ± 0.77	0.29 ± 0.6	
Pioglitazone	7.45 ± 0.91	7.18 ± 0.72	0.27 ± 0.47	
Acarbose	7.67 ± 0.75	7.71 ± 0.67	-0.04 ± 0.28	
Combination therapy				
Vildagliptin + Pioglitazone	7.8 ± 0.53	7.13 ± 0.74	0.67 ± 0.66	
Vildagliptin + Metformin	8.08 ± 0.83	7.35 ± 0.64	0.73 ± 0.37	

And vildagliptin alone group showing a large range of mean ± SD decrease (0.5 ± 0.35). In acarbose group post-treatment day (7.71 ± 0.67) value is greater than that of pre-treatment day (7.67 ± 0.75) value, it shows negative mean decrease (-0.04 ± 0.28)

that means it have no effect on blood glucose level. Ahre´n *et al., 2010* conducted study also shows a better control of vildagliptin monotherapy on HbA1c.

In combination therapy vildagliptin- metformin combination shows greater degree of mean decrease (0.73 ± 0.37) than that of vildagliptin+pioglitazone (0.67 ± 0.66) group. In total group comparison vildagliptin- metformin then vildagliptin+pioglitazone are beneficial than that of vildagliptin alone. *Ahrén* 2008, his 52 week study also shows a reducion HbA1c levels by 0.65%–1.1% (baseline HbA1c 7.2–8.7%) mean decrease of P (0.0001) value is significant.

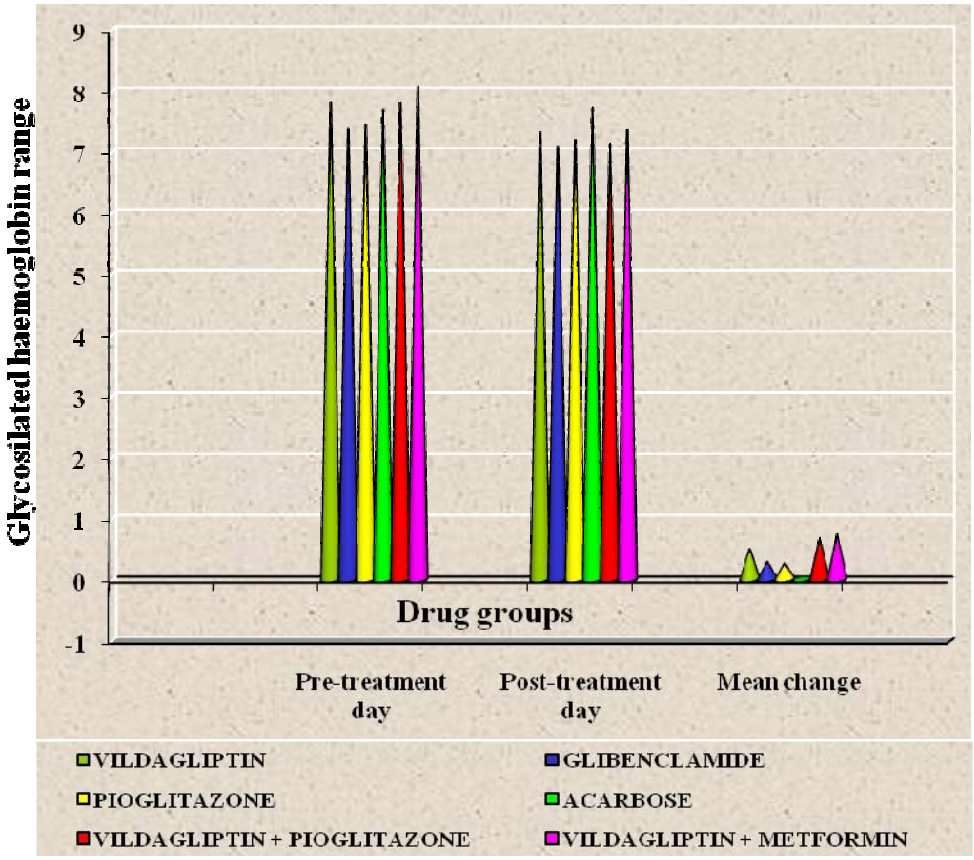


Figure. 6 Glycosylated haemoglobin level

Serum Low density lipoprotein level (LDL) data:-

LDL of two hundred and seven (207) patients observed and recorded the values of first (initial therapy) visit and third (final therapy) visit. Data is mentioned in the Table-7 & Figure 7, in that we get the initial, final & their changes of the LDL in (mean ± SD) values. As we know the anti-diabetics doesn't have a major role on the lipid profiles but also the show some effects. In monotherapy group Glibenclamide &Pioglitazone shows a mild mean decrease of LDL (1.4 ± 8.7) & (1.3 ± 5.9) as respectively, But in case of vildagliptin & acarbose shows a mild negative decrease (increase) of LDL (-1.2 ± 9.4) & (-1.3 ± 4.7) as respectively.

Table.7 Lipid profile –serum low density lipoprotein

Group	**Low density lipoprotein(LDL)**			P value
	Initial therapy	**Final therapy**	**Change in LDL**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Monotherapy				
Vildagliptin	115.6 ± 11.3	116.8 ± 11.4	-1.2 ± 9.4	
Glibenclamide	108 ± 17.0	106.6 ± 15.2	1.4 ± 8.7	
Pioglitazone	113.3 ± 17.1	112.0 ± 16.1	1.3 ± 5.9	0.0985
Acarbose	113.1 ± 11.8	114.4 ± 10.1	-1.3 ± 4.7	Not
Combination therapy				Significant
Vildagliptin + Pioglitazone	123.0 ± 13.9	121.7 ± 13.4	1.3 ± 5.3	
Vildagliptin + Metformin	120.4 ± 18.2	115.9 ± 12.3	4.5 ± 9.0	

Study of Yosefy *et al., 2004* on thiazonidinediones (pioglitazone) shows improve low density lipoprotein (LDL) particle size by converting the small, dense particles into larger, less atherogenic ones

In combination therapy vildagliptin+metformin combination shows higher ran- ge of mean LDL (4.5 ± 9.0) decrease than that of vildagliptin+pioglitazone (1.3 ± 5.3) combination therapy group. *M.G. Wulffele et al*., *2004*, Study shows LDL lowering effect of metformin. In total group comparison Vildagliptin- metformin combination (4.5 ± 9.0) shows better mean LDL decrease than that of other combination and mono therapy groups, the mean LDL decrease P (0.0985) value of 6 sub classes are not significant.

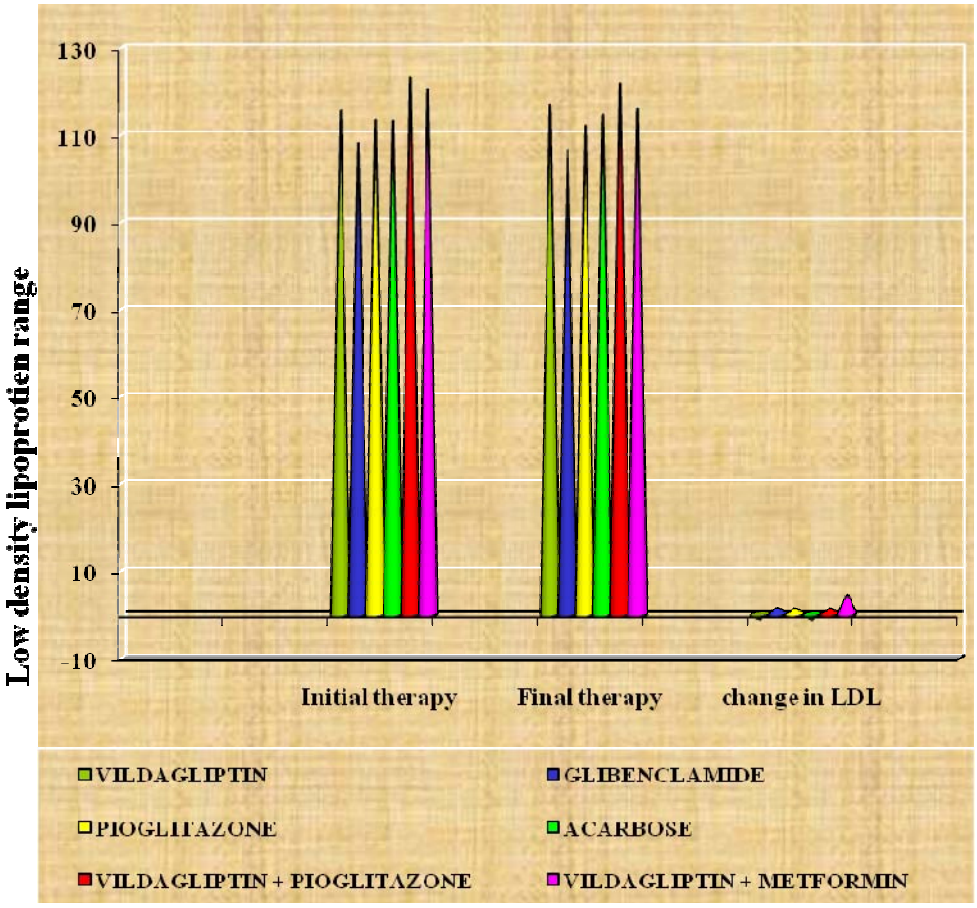


Figure . 7 Low density lipoprotein level data

Very low density lipoprotein (VLDL):-

VLDL of two hundred and seven (207) patients observed and recorded the values of first (pre-treatment) visit and third (Post-treatment) visit. Data is mentioned in the Table-8 & Figure 8, in that we get the pre, post & their changes of the VLDL in (mean ± SD) values. As we know the anti-diabetics doesn't have a major role on the lipid profiles, especially VLDL but also the show some effects as shown in below.

Table 8- Very low density lipoprotein level data

Group	Very low density lipoprotein(VLDL)			P value
	Pre-treatment	Post-treatment	Mean change	
	Mean ± SD	Mean ± SD	Mean ± SD	
Monotherapy				
Vildagliptin	31.0 ± 5.1	32.5 ± 4.6	-1.5 ± 3.8	
Glibenclamide	28.2 ± 6.2	29.8 ± 4.7	-1.6 ± 4.0	
Pioglitazone	32.3 ± 5.1	30.9 ± 5.2	1.4 ± 3.3	
Acarbose	34.2 ± 5.3	33.8 ± 6.0	0.3 ± 3.9	**0.0009**
Combination therapy				**Significant**
Vildagliptin + Pioglitazone	34.9 ± 5.0	34.9 ± 3.6	-0.09 ± 3.2	
Vildagliptin + Metformin	34.5 ± 10.1	33.4 ± 8.3	1.1 ± 3.2	

In monotherapy group pioglitazone (1.4 ± 3.3) & acarbose (0.3 ± 3.9) shows (mean ± SD) decrease of VLDL, but in case of vildagliptin & glibenclamide shows negative decrease of (mean ± SD) of VLDL (-1.5 ± 3.8) & (-1.6 ± 4.0) as

respectively. Schernthaner *et al., 2004,* conducted study on effect of pioglitazone on VLDL also shows the slight VLDL lowering effect.

In combination therapy group vildagliptin+metformin group shows mean decrease VLDL (1.1 ± 3.2), M.G. Wulffele´ *et al.,* 2004, conducted a study on metformin also shows reduced triglycerides (is proportional to VLDL) by 0.19 mmol $L)^{-1}$, but in case of Vildagliptin+pioglitazone group shows an negative range of decrease of mean VLDL (-0.09 ± 3.2). The P value of mean ± SD value is significant (0.0009) for all 6 groups

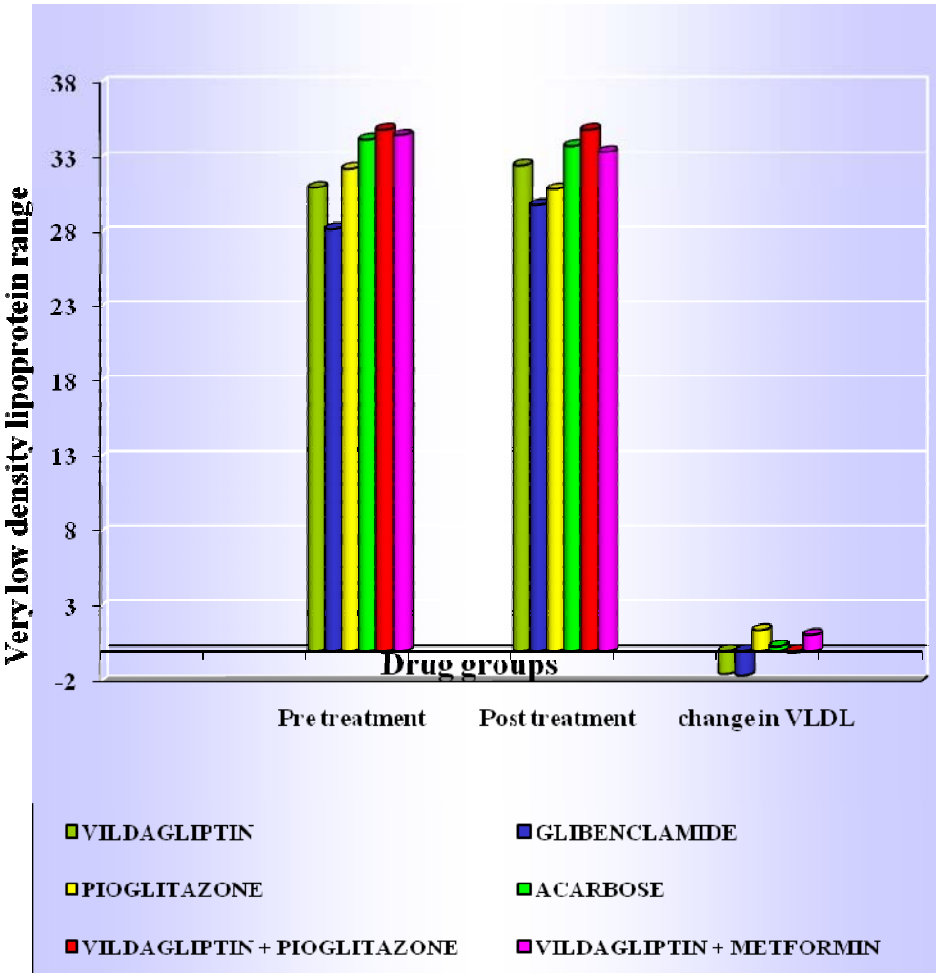


Figure.8 Very low density lipoprotein level

Serum high density lipoprotein level (HDL):-

HDL of two hundred and seven (207) patients observed and recorded the values of first (pre-treatment) visit and third (Post-treatment) visit. Data is mentioned in the Table-9 & Figure 9, in that we get the pre, post & their changes of the HDL in (mean ± SD) values. As we know HDL is the good cholesterol, >40 mmol/l is considered as normal, because it is essential for some of body activities and production. In monotherapy group pioglitazone from the pre-treatment (42.6 ± 5.1) value post-treatment (44.6 ± 5.2) values shows a positive (mean ± SD) increase of HDL (2.0 ± 2.8).

Table.9 Serum high density lipoprotein chart

Group	High density lipoprotein(HDL)			P value
	Pre-treatment	**Post-treatment**	**Mean increase**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Monotherapy				
Vildagliptin	44.1 ± 5.7	40.1 ± 4.9	-4.0 ± 4.4	
Glibenclamide	42.6 ± 4.3	42 ± 3.1	-0.7 ± 3.9	
Pioglitazone	42.6 ± 5.1	44.6 ± 5.2	2.0 ± 2.8	**0.0001**
Acarbose	43.4 ± 3.5	42.7 ± 2.3	-0.7 ± 3.2	**Significant**
Combination therapy				
Vildagliptin + Pioglitazone	43.9 ± 4.4	42.4 ± 3.1	-1.5 ± 3.8	
Vildagliptin + Metformin	45.0 ± 5.3	43.7 ± 4.4	-1.3 ± 3.5	

Study of Naoumova *et al*.,2007,conducted a study of Pioglitazone shows a significant HDL improvement effect. .But in case of other groups like vildagliptin (-4.0 ± 4.4), glibenclamide (-0.7 ± 3.9) & acarbose (-0.7 ± 3.2) shows negative increase and it is not beneficial.In case of combination therapy group both combination of vildagliptin are showing HDL lowering effect, in vildagliptin+metfomin group (-1.3 ± 3.5) is better than that of vildagliptin+pioglitazone (-1.5 ± 3.8) group in the HDL lowering effect. In both group comparisons vildagliptin+metfomin is better than vildagliptin+pioglitazone & vildagliptin Monotherapy. The P values of mean ± SD increase value (0.0001) of all six groups are significant.

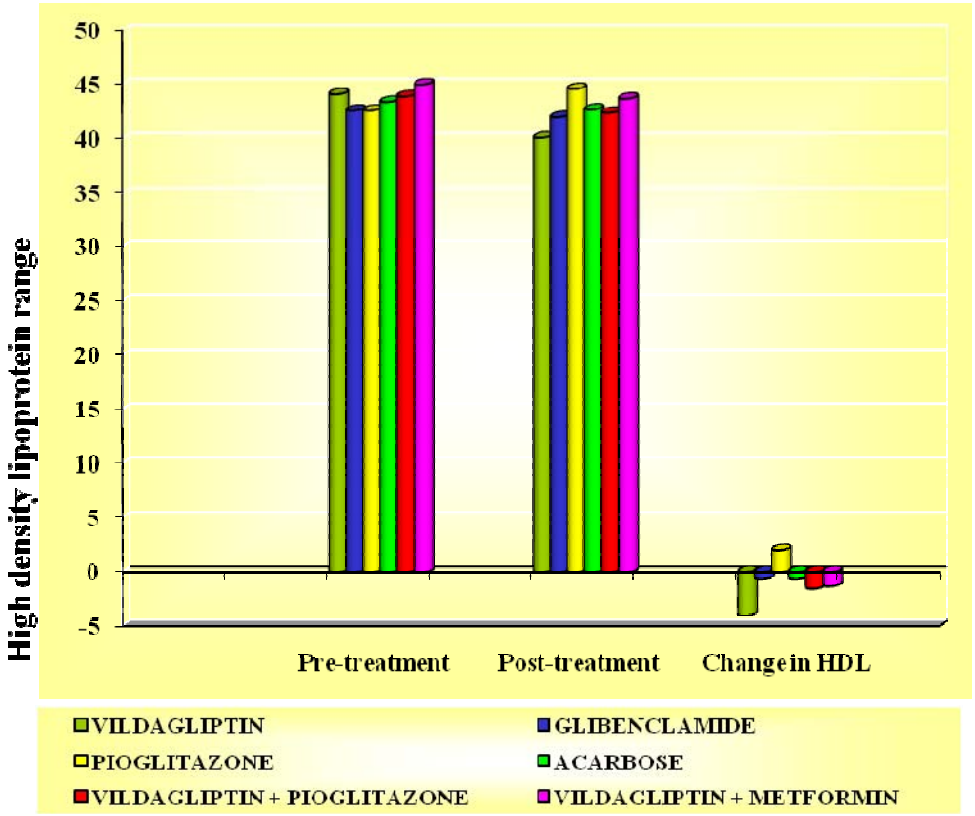


Figure 11- Mean High density lipoprotein level.

Serum Total cholesterol level data (TC):-

Total cholesterol of two hundred and seven (207) patients observed and recorded the values of first (Initial treatment) visit and third (Final treatment) visit. Data is mentioned in the Table-10 & Figure 10, in that we get the pre, post & their changes of the Total cholesterol in (mean ± SD) values. Most of the dieticians recommend to check the total cholesterol at least 6 month intervals, because of its high level total cholesterol leads cardiac risk. >200 mg/dl total cholesterol is considered as hyper cholesterolemia.

Table .10 Total cholesterol chart

Group	Total cholesterol(TC)			P value
	Initial treatment	Final treatment	Change in TC	
	Mean ± SD	Mean ± SD	Mean ± SD	
Monotherapy				
Vildagliptin	190.6 ± 15.6	189.2 ± 15.9	1.4 ± 11.5	
Glibenclamide	178.0 ± 19.6	178.5 ± 18.4	-0.4 ± 9.7	
Pioglitazone	188 ± 20.0	187.4 ± 18.5	0.6 ± 6.3	
Acarbose	196.5 ± 21.7	190.9 ± 12.7	5.5 ± 12.8	**0.0216**
Combination therapy				**Significant**
Vildagliptin +Pioglitazone	203.9 ± 22.4	198 ± 16.2	5.9 ± 13.8	
Vildagliptin + Metformin	201.6 ± 29.7	190.3 ± 25.3	11.9 ± 22.9	

In monotherapy group vildagliptin (-1.4 ± 11.5) & glibenclamide (-0.4 ± 9.7) shows a small (mean ± SD) negative decrease of total cholesterol, Pioglitazone (0.6 ±

6.3) and acarbose (5.5 ± 12.8) shows a positive decrease of total cholesterol. Study of Naoumova *et al*., 2007, of pioglitazone shows the lowering of total cholesterol and total cholesterol HDL cholesterol ratio decrease. In combination therapy group vildagliptin+metformin (11.9 ± 22.9) shows greater decrease (mean ± SD) than that of vildagliptin+pioglitazone (5.9 ± 13.8) combination. M.G. Wulffele´ *et al.,* 2004, conducted a study on metformin also shows reduced total cholesterol. The P value of mean decrease rates (0.0216) is significant.

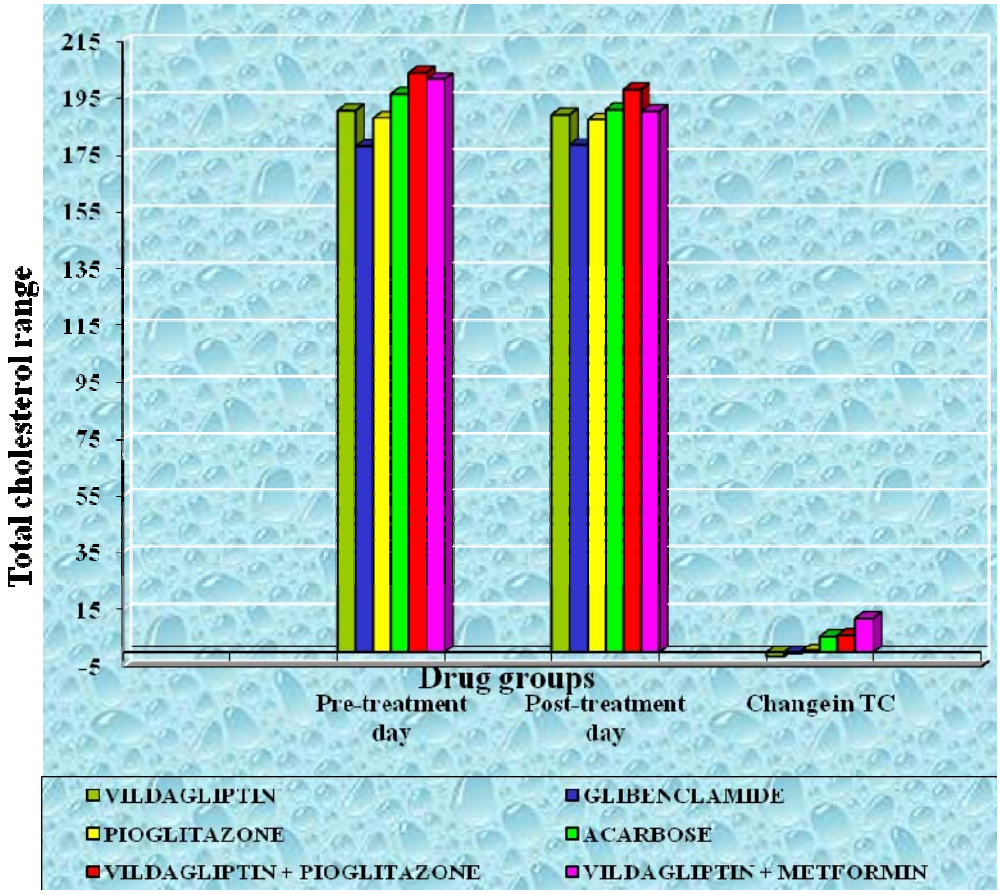


Figure 10- Total cholesterol level data.

Hepatic safety profile-(LFTs or LFs), are groups of clinical biochemistry laboratory blood assays designed to give information about the state of a patient's liver. The parameters measured include PT/INR, a PTT, albumin, billirubin (direct and indirect) and others. According to some, liver transaminases (AST/ALT (SGOT/SGPT) are *not* liver function tests, but are biomarkers of liver injury in a patient with some degree of intact liver function. Most liver diseases cause only mild symptoms initially, but it is vital that these diseases be detected early. Hepatic (liver) involvement in some diseases can be of crucial importance. This testing is performed by a medical technologist on a patient's serum or plasma sample obtained by phlebotomy. Several biochemical tests are useful in the evaluation and management of patients with hepatic dysfunction. These tests can be used to (1) detect the presence of liver disease, (2) distinguish among different types of liver disorders, (3) gauge the extent of known liver damage, and (4) follow the response to treatment. Some or all of these measurements are also carried out (usually about twice a year for routine cases) on those individuals taking certain medications.

Alanine transaminase (ALT-7-56 IU/L) - also called serum glutamic pyruvate transaminase (SGPT) is an enzyme present in hepatocytes (liver cells). When a cell is damaged, it leaks this enzyme into the blood, where it is measured.

Aspartate transaminase (AST 5-40 IU/L)- also called serum glutamic oxaloacetic transaminase (SGOT) is similar to ALT in that it is another enzyme associated with liver parenchymal cells. It is raised in acute liver damage, but is also present in red blood cells and cardiac and skeletal muscle and is therefore not specific to the liver. The ratio of AST to ALT is sometimes useful in differentiating between causes of liver damage.

Hepatic safety profile - Alanine transaminase (ALT):-

ALT of two hundred and seven (207) patients observed and recorded the values of first (pre-treatment day) visit and third (Post-treatment day). Data are recorded in the Table-11 & Figure 11, in that we get the pre, post & their changes of the ALT in (mean ± SD) values. Most of the diabeticians recommend checking the ALT at least one year intervals, its small range variation not considered as any hepatic disorder, it's twice/trice will indicate hepatic toxicity or disorder.

Table 11-Alanine transaminase level data

Group	**Alanine transaminase(ALT)**			**P value**
	Pre-treatment	**Post-treatment**	**Mean change**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Monotherapy				
Vildagliptin	26.5 ± 8.0	28.5 ± 7.7	1.9 ± 2.1	
Glibenclamide	27.5 ± 6.6	27.7 ± 6.7	0.2 ± 1.4	
Pioglitazone	28.8 ± 9.4	29.3 ± 9.6	0.5 ± 1.0	**0.0001**
Acarbose	25.8 ± 5.6	25.8 ± 5.3	0 ± 1.0	**Significant**
Combination therapy				
Vildagliptin + Pioglitazone	26.4 ± 6.5	27.9 ± 5.9	1.5 ± 2.1	
Vildagliptin + Metformin	26.2 ± 6.7	26.2 ± 6.8	0.04 ± 0.7	

In the monotherapy group vildagliptin (1.9 ± 2.1) shows more increase than that of other groups, acarbose (0 ± 1.0) shows least increase of ALT. Glibenclamide (0.2 ± 1.4) & pioglitazone (0.5 ± 1.0) also shows a slight increase of AST, Tolman K G *et al*., 2009, conducted a 12 week study of pioglitazone & glibenclamide shows the slight increase of ALT. In combination therapy group vildagliptin+pioglitazone (1.5 ± 2.1) shows more increase than that of vildagliptin- metformin (0.04 ± 0.7), that means vildagliptin+metformin is beneficial than that of vildagliptin+pioglitazone & vildagliptin monotherapy. The P value mean decreases (0.0001) of six groups are significant.

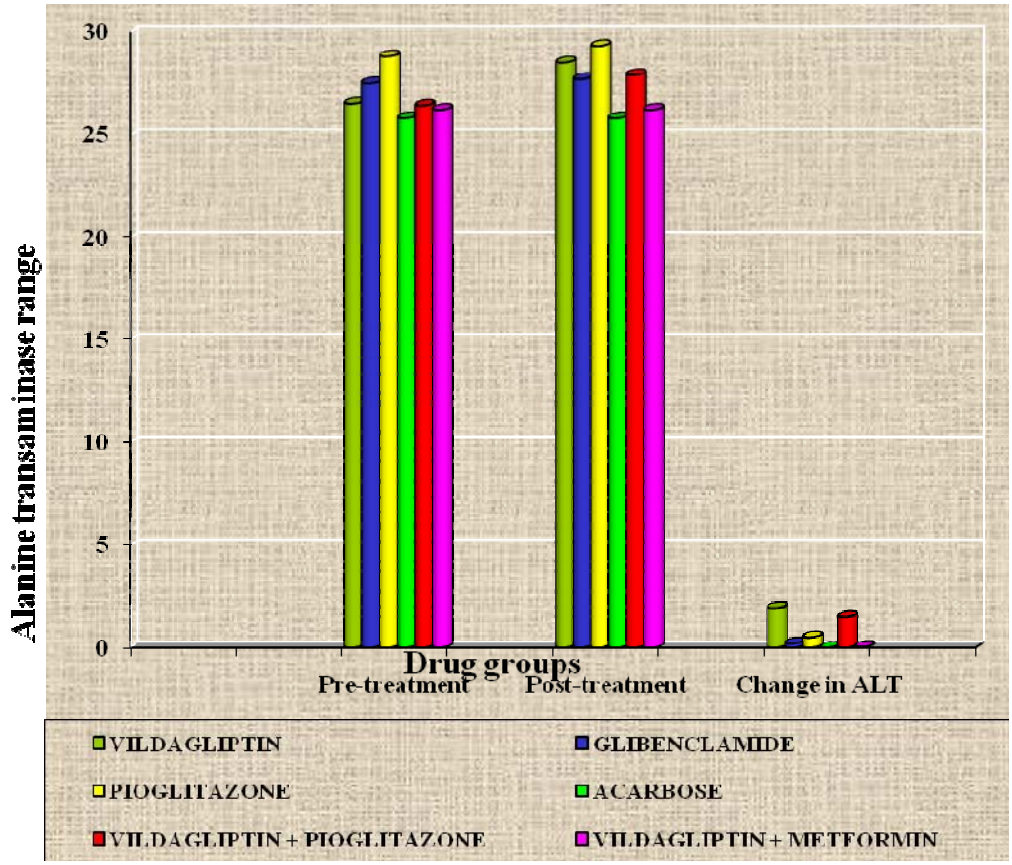


Figure.11 Alanine transaminase level data

Hepatic safety profile – Aspartate transaminase (AST):-

AST 207 patients observed and recorded the values of first (pre-treatment) visit and third (Post-treatment) visit. Data are recorded in the Table-12 & Figure 12, in that we get the pre, post & their changes of the AST in (mean ± SD) values. Most of the diabeticians recommend to check the AST at least one year intervals, Its value or AST-ALT ratio is very helpful to check the hepatic disorder, it's twice/trice of the upper limit of the normal values considered as hepatic disorders or toxicity.

Table.12 Aspartate transaminase level data.

Group	Aspartate transaminase(AST)			P value
	Pre-treatment	Post-treatment	Change in AST	
	Mean ± SD	Mean ± SD	Mean ± SD	
Monotherapy				
Vildagliptin	23.3 ± 6.6	24.2 ± 6.6	0.9 ± 1.7	
Glibenclamide	23.5 ± 5.2	23.7 ± 5.2	0.2 ± 1.4	
Pioglitazone	24.5 ± 8.1	25.0 ± 8.0	0.5 ± 1.3	**0.0004**
Acarbose	20.8 ± 3.8	22.1 ± 4.9	1.3 ± 1.5	**Significant**
Combination therapy				
Vildagliptin + Pioglitazone	23.5 ± 5.9	24.7 ± 5.2	1.2 ± 2.2	
Vildagliptin + Metformin	23.4 ± 6.6	23.3 ± 6.3	-0.1 ± 0.9	

In monotherapy group acarbose (1.3 ± 1.5) shows the highest (mean ± SD) rate of increase, Study of M Malaguarnera *et al*., 1999, on acarbose shows the slight increase

of AST. Vildagliptin (0.9 ± 1.7) is the second most AST increase in the monotherapy group, but these increases are very milder range & they doesn't mean any hepatic damages (liver toxicity). In combination therapy group vildagliptin+pioglitazone (1.2 ± 2.2) shows more increase than that of vildagliptin+ metformin (-0.1 ± 0.9) and vildagliptin+ metformin group shows a milder decrease of AST & it is a beneficiary effect, that means vildagliptin+metformin is beneficial than that of vildagliptin+pioglitazone & vildagliptin monotherapy. The P value mean decrease (0.0001) of six groups is significant.

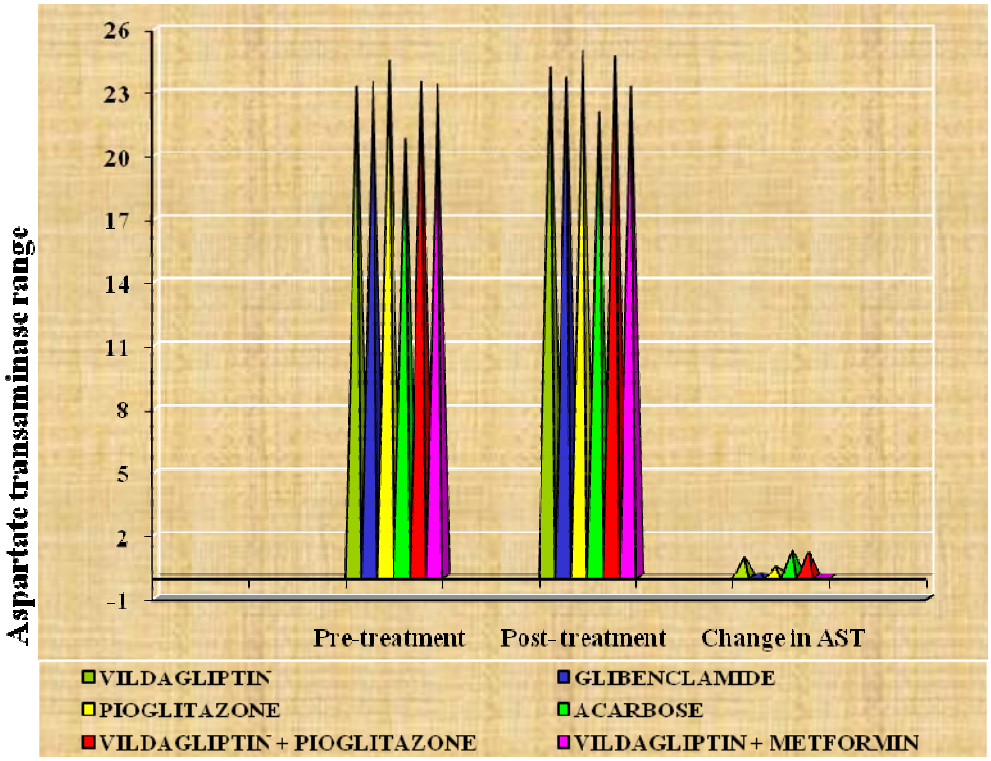


Figure. 12 Aspartate transaminase level data

Adverse drug reaction report:-

Adverse drug reaction of two hundred and seven (207) patients are checked during their regular visit, mostly adverse drug reaction report are collected in the third visit. Most of the adverse drug reaction reported here are expectable types. Weight gain, abdominal pain, constipation, diarrhea, nausea, muscle pain, hypoglycemia, hyperglycemia are the most common reported adverse drug reactions.

Table 13-Adverse drug reaction (ADR) summary and most common ADRs

Adverse drug Reaction	No. of incidences in adverse reaction & its percentage															
	Monotherapy										Combined therapy					
	Vild (34)		Gli (47)		Pio (39)		Acrbs (13)		Total (133)		Vil+Pio (34)		Vil+Met (40)		Total (74)	
Weight gain	10	29.4	6	12.8	15	38.5	-	-	31	23.3	13	38.2	1	2.5	14	18.9
Abdominal Pain	-	-	-	-	1	2.6	-	-	1	0.8	-	-	1	2.5	1	1.4
Constipation	-	-	4	8.5	3	7.7	1	7.7	8	6.0	1	2.9	3	7.5	4	5.4
Diarrhea	1	2.9	2	4.3	-	-	-	-	3	2.3	1	2.9	1	2.5	2	2.7
Nausea	-	-	2	4.3	-	-	-	-	2	1.5	1	2.9	-	-	1	1.4
Muscle pain	-	-	-	-	1	2.6	-		1	0.8	-	-	-	-	-	-
Hypo glycemia	-	-	3	6.4	2	5.1	-	-	5	3.8	6	17.6	-	-	6	8.1
Hyper glycemia	-	-	2	4.3	1	2.6	5	38.5	8	6.0	1	2.9	-	-	1	1.4
Any one complaint	11	32.4	19	40.4	22	56.4	6	46.2	58	43.6	21	61.8	5	12.5	27	36.5

5 cases had more than one complication.

The weight gain 45 (21.73%) is the most seeing adverse drug reaction, muscle pain 1 (0.48%) is the least reported one. From the total two hundred and seven (207) patients 85 (41.06%) patients shows any one of the adverse drug reaction, and 5 (2.41) showing more than one adverse drug reaction.

In monotherapy group vildagliptin shows lowest 11 (32.4%) percentage of the adverse drug reaction, study of Schweizer *et al*., 2011, also shows the drug-related AEs Were seen with a lower frequency in vildagliptin-treated patients (15.7%) and the pioglitazone shows the highest 22(56.4%) percentage of adverse drug reaction. In the combination therapy group Vildagliptin+metformin shows least 5(12.5%) adverse drug reaction than that of Vildagliptin+pioglitazone group.

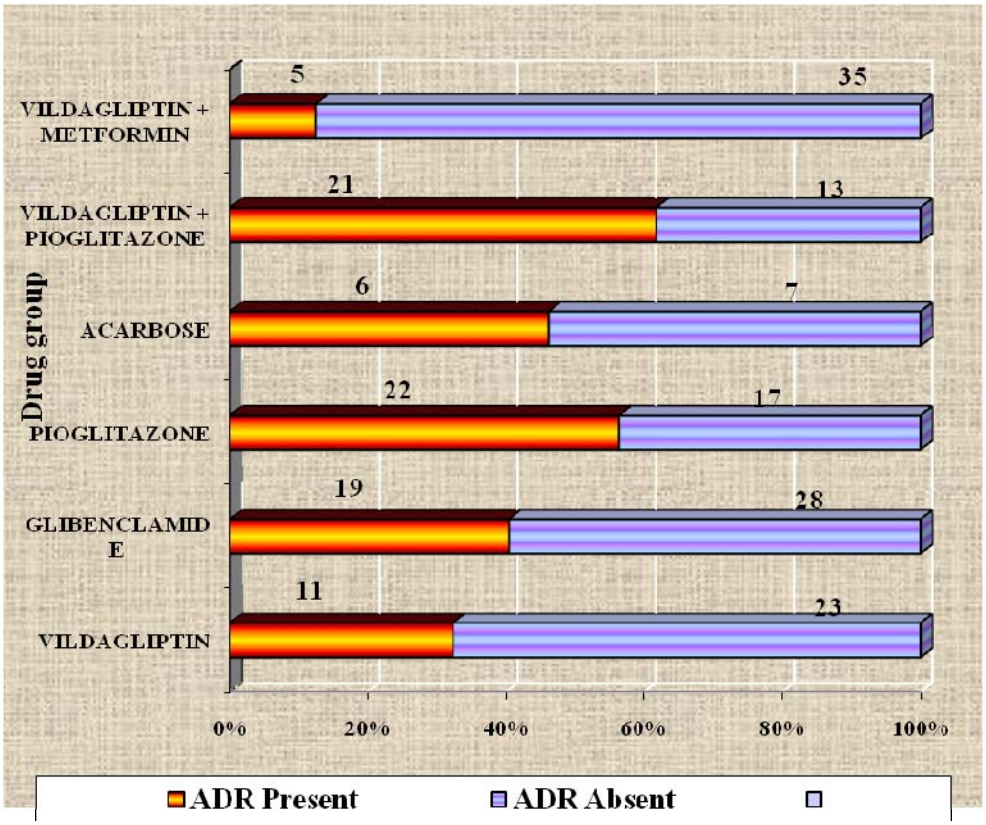


Figure.13 Adverse drug reaction (ADR) summary and most common ADRs

DISCUSSION

All together two hundred and seven (207) patients were enrolled in to the study over a period of 10 months, In that males 133 (64.25%) and females 74 (35.74%). The total patients are classified in to two groups based on the number of drug consumption (Monotherapy & Combination therapy) in monotherapy group males 86(64.7%) & females 47(35.3%) are there out of 133,in combination therapy consist of 74 patients in that 47(63.3%) males & 27 females(36.5%). This study shows the prevalence of diabetics in male than that of female.

Based on age wise distribution patients are divided in to five age groups. They are 35-45 year, 46-55 year, 56-65 years, 66-75 years, and 76-85 years. In that more patients 67 (32.36%) are in age group of 46-55 years & 56-65 years in each group. Usually 50-70 years are more prominent age group in type 2 diabetes, because these age group food consumption and food utilization ratio are entirely different. It makes these age group is more prominent than other groups.

Among the study population 176 (85.02%) have family history of diabetes mellitus & 31(14.97%) doesn't with family history. Diabetes is highly depend on family history & hereditary.

Body mass index denote the body weight-height ratio, the optimum BMI is considered as 18-22 kg/m^2. The drug which has the BMI lowering effect is highly beneficial in obese & over weight patients; in our monotherapy group vildagliptin group only shows positive weight (0.24 ± 0.52) decrease, other groups doesn't shows any weight lowering effect. In combination therapy Vildagliptin + Metformin group

(0.41 ± 0.53) only shows greater decline of body weight, but not by Vildagliptin+ Pioglitazone.

A good anti-diabetic drug shows considerable blood sugar lowering effect without causing hypoglycemia. On the basis of fasting blood sugar (FBS) In our monotherapy all groups except acarbose shows considerable lowering of blood sugar, compare to other group vildagliptin shows higher decrease (35.0 ± 22.8) range. In combination therapy both groups shows fasting blood sugar lowering effect, vildagliptin + metformin shows more (36.5 ± 27.6) effect than vildagliptin + pioglitazone (31.8 ± 47.4).

Random blood sugar (RBS) lowering also one of the identical parameter to check the efficacy of an anti- diabetic drug. In monotherapy group vildagliptin shows higher degree (79.1 ± 42.2) of random blood sugar (RBS) lowering effect than that of other group, in combination therapy both are highly effective, but also vildagliptin + metformin shows more (85 ± 47.2) effect than vildagliptin + pioglitazone (58.7 ± 74.4).

Glycosylated haemoglobin (HbA1c) is the most relevant & prominent parameter to assess the efficacy and effectiveness of an anti diabetic drug. But it not widely used because of its cost; it is very useful to detect the blood sugar level of a period time. In our monotherapy group all group except acarbose shows significant decrease of HbA1c, in that vildagliptin (0.5 ± 0.35) shows the greater decreasing effect. In combination therapy vildagliptin + metformin (0.73 ± 0.37) shows greater effect than that of vildagliptin + pioglitazone (0.67 ± 0.66).

As we know the anti-diabetics doesn't have a major role on the lipid profiles but also the show some effects. In monotherapy group Glibenclamide &Pioglitazone shows a mild mean decrease of LDL (1.4 ± 8.7) & (1.3 ± 5.9) as respectively, But in case of vildagliptin & acarbose shows a mild negative decrease (increase) of LDL (-1.2 ± 9.4) & (-1.3 ± 4.7) as respectively. In combination therapy vildagliptin + metformin combination shows higher range of mean LDL (4.5 ± 9.0) decrease than that of vildagliptin + pioglitazone (1.3 ± 5.3) combination therapy group.

The VLDL change of our study shows as follows in monotherapy group; pioglitazone (1.4 ± 3.3) & acarbose (0.3 ± 3.9) only shows (mean ± SD) decrease of VLDL, but in case of vildagliptin & glibenclamide shows negative decrease of (mean ± SD) of VLDL (-1.5 ± 3.8) & (-1.6 ± 4.0) as respectively. In combination therapy group vildagliptin+metformin group shows mean decrease VLDL (1.1 ± 3.2).

High density lipoprotein is considered as good cholesterol, it is one of the energy donor of our body, its increasing effect is considered as one of the beneficial effect. In our monotherapy study pioglitazone shows a positive (mean ± SD) increase of HDL (2.0 ± 2.8). but in combination therapy group both combination of vildagliptin are showing HDL lowering effect.

Increased total cholesterol level (>200 mg/dl) leads to high cardiac risk, its lowering effect is highly beneficial. In our monotherapy group only vildagliptin (1.4 ± 11.5) shows significant TC decrease. In combination therapy group vildagliptin + metformin & vildagliptin + pioglitazone shows TC lowering effect as (11.9 ± 22.9) & (5.9 ± 13.8) respectively.

Hepatic safety profile is one of the major safety profiles, because the entire drug metabolism is takes place at liver only. For these purpose Aspartate transaminase (AST) & Alanine transaminase (ALT) are done at specific intervals. But its twice or trice amount of the normal value is considered as hepatic toxicity or damage. In our monotherapy study all drug groups except acarbose (acarbose shows neutral effect on ALT) shows increased value of AST & ALT.

Adverse drug reactions are the unwanted effects of a drug in its therapeutic doses. In our study; monotherapy group vildagliptin shows lowest 11 (32.4%) percentage of the adverse drug reaction. In the combination therapy group Vildagliptin+metformin shows least 5(12.5%) adverse drug reaction than that of Vildagliptin+pioglitazone group.

CONCLUSION

DPP-4 inhibition is efficient in reducing Glycosylated haemoglobin (HbA1c), fasting blood sugar (FBS) & random blood sugar (RBS). In the monotherapy Setting, DPP-4 has produced a reduction of approximately 0.5±0.35 in HbA1c, 35± 22.8 in FBS & 79.1± 42.2 in RBS are shown in different age and sex population & it shows a decreasing effect of BMI, serum lipid profile – high density lipoprotein (HDL) & total cholesterol (TC). Vildagliptin shows a slight increasing effect of LDL, VLDL. DPP-4 inhibition is also safe and tolerable is because it shows very slight increase of Hepatic safety profile AST (0.9±1.7) & ALT (1.9 ± 2.1), and also it shows less (11) number of Adverse drug reaction than that of other group.

In combination therapy setting, Vildagliptin+metformin shows more beneficial effect than that of Vildagliptin+pioglitazone in lowering effect of FBS, RBS, HbA1c, BMI, Lipid profile LDL, VLDL, TC, Hepatic safety profile ALT, AST & least number of Adverse effect.

Therefore, DPP-4 inhibition is a new, efficient and tolerable treatment of type 2 Diabetes that may improve the disease process. It may be suggested that a primary place for DPP-4 inhibition is as a first-line treatment since it is efficient, safe, tolerable and orally active. Furthermore, the efficiency of DPP-4 inhibition in combination both with metformin and with TZDs suggests that it may be useful as combination therapy.

Encouragingly, the safety and tolerability data from combination studies show that addition of a DPP-4 inhibitor to the ongoing monotherapy regimen has similar incidences of adverse effects versus monotherapy. Furthermore, there is a low incidence of hypoglycemia in the combination regimens. Long-term studies are now warranted to show the durability and long-term safety of this approach to treat type 2 diabetes.

FUTURE RECOMMANDATION

- In monitoring of glycemic control is performed by the patients measuring their own plasma or blood glucose with meters and by laboratory analysis of HbA_{1c}. The potential roles of noninvasive glucose monitoring, genetic testing, and measurement of auto antibodies, urine albumin, insulin, proinsulin, C-peptide, and other analytes are addressed.

- Lifestyle influences the development of type 2 diabetes. Obesity tends to run in families, and families tend to have similar eating and exercise habits ,so recommend to patients to follow healthy diet & regular exercise

- Screening Recommendations for Asymptomatic Persons those have above 45 year age / having BMI $\geq$ 27 kg/m^2 (or) HDL cholesterol level $\leq$35 mg per dL (0.90 mmol per L) and/or triglyceride level $\geq$ 250 mg per dL (2.83 mmol per L)(or) Hypertensive ($\geq$ 140/90 mm Hg) recommend them to test and repeat every three year.

- Prepare diet plan for a diabetic is based on height, weight, age, sex, physical activity and nature of diabetes. While planning diet, the dietician has to consider complications such as high blood pressure, high cholesterol levels

- Like diabetes, high blood pressure can damage our blood vessels. High cholesterol is a concern, too, since the damage is often worse and more rapid when you have diabetes. When these conditions team up, they can lead to a heart attack, stroke or other life-threatening conditions.

- Schedule yearly and regular kidney function to detect diabetic nephropathy, because it is one of the major diabetic complications.

- Advice to check hepatic functional test to patients those are taking diabetics drugs especially vildagliptin.

- Diabetes may leave you prone to gum infections. Brush your teeth at least twice a day, floss your teeth once a day, and schedule dental exams at least twice a year. Consult your dentist right away if your gums bleed or look red or swollen.

- Consider a daily aspirin- Aspirin reduces blood's ability to clot. Taking a daily aspirin can reduce your risk of heart attack and stroke.

- Recommend to control stress, stress will prevent insulin from working properly, which only makes matters worse. To take control, set limits. Prioritize your tasks. Learn relaxation techniques. Get plenty of sleep.

- Incidence of hypoglycemia is more with pioglitazone, so recommend the patient to take food as soon as possible while taking medicine.

- Recommend the obese patient to include metformin to their drug to reduce weight vildagliptin taking patients those having impaired LDL,VLDL,HDL, recommend to add metformin.

- The increased study population need to get more clear data

- To get the exact ADRs & Safety profile need more time period to study.

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